```
=> file registry
FILE 'REGISTRY' ENTERED AT 12:06:09 ON 28 DEC 2007
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   27 DEC 2007  HIGHEST RN 959655-61-9
DICTIONARY FILE UPDATES:  27 DEC 2007  HIGHEST RN 959655-61-9

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> file zcaplus
FILE 'ZCAPLUS' ENTERED AT 12:06:13 ON 28 DEC 2007
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FILE COVERS 1907 - 28 Dec 2007  VOL 148 ISS 1
FILE LAST UPDATED: 27 Dec 2007  (20071227/ED)

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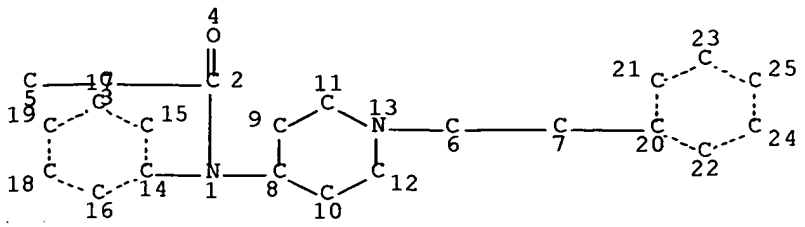
  This file contains CAS Registry Numbers for easy and accurate
  substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'ZCAPLUS' FILE

=> d stat que L92
L92           4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI EN?/AU


=> d stat que L95
L13             STR
```



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

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L15          70 SEA FILE=REGISTRY FAM FUL L13
L92           4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI EN?/AU
L95           1 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L15 AND L92


=> d stat que L96
L40      195334 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  HPLC/BI
L91         121 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI E/AU
L96           0 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L91 AND L40


=> d stat que L97
L44      187446 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L91         121 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI E/AU
L97           0 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L91 AND L44


=> d stat que L98
L31        70356 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  REVERS?/BI (W) PHASE#/BI
L91         121 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI E/AU
L98           0 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L91 AND L31


=> d stat que L99
L40      195334 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  HPLC/BI
L92           4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI EN?/AU
L99           1 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L92 AND L40


=> d stat que L100
L44      187446 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L92           4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI EN?/AU
L100          2 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L92 AND L44


=> d stat que L101
L31        70356 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  REVERS?/BI (W) PHASE#/BI
L92           4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI EN?/AU
L101          4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L92 AND L31
```

```
=> s L92 or L95 or L96-L101
L106          4 L92 OR L95 OR (L96 OR L97 OR L98 OR L99 OR L100 OR L101)

=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 12:07:06 ON 28 DEC 2007
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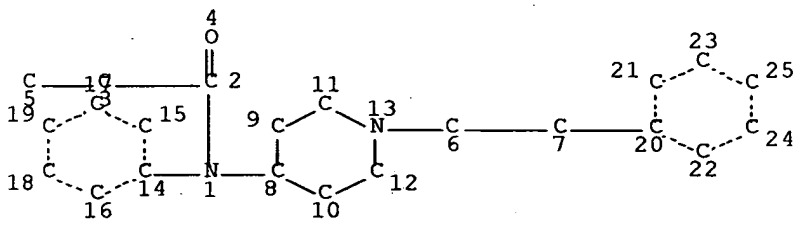
```
FILE COVERS 1907 - 28 Dec 2007  VOL 148 ISS 1
FILE LAST UPDATED: 27 Dec 2007  (20071227/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d stat que L105
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                  2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13             STR
```



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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L15           70 SEA FILE=REGISTRY FAM FUL L13
```

```
L16          31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19          36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20          13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L45      132461 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LIQUID CHROMATOGRAPHY+NT,OLD/C
                T
L46        4765 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L23
L47          71 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L45 AND L46
L48      187446 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L49         100 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L46 AND L48
L50         113 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L47 OR L49
L51      859647 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PURIF?/BI
L52     1536035 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEPARAT?/BI
L53           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L50 AND L51
L54          32 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L50 AND L52
L55      195334 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HPLC/BI
L57          90 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L46 AND L55
L58           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L57 AND L51
L59          22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L57 AND L52
L91         121 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI E/AU
L92           4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI EN?/AU
L105          1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L91 OR L92) AND (L53 OR L54
                OR L58 OR L59)


=> file uspatfull
FILE 'USPATFULL' ENTERED AT 12:07:17 ON 28 DEC 2007
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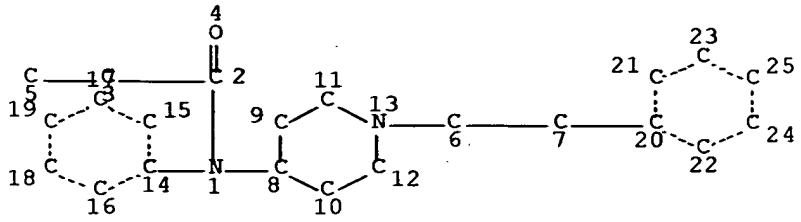
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Dec 2007 (20071227/PD)
FILE LAST UPDATED: 27 Dec 2007 (20071227/ED)
HIGHEST GRANTED PATENT NUMBER: US7313828
HIGHEST APPLICATION PUBLICATION NUMBER: US2007300346
CA INDEXING IS CURRENT THROUGH 27 Dec 2007 (20071227/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Dec 2007 (20071227/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2007
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2007


=> d stat que L103
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13             STR
```



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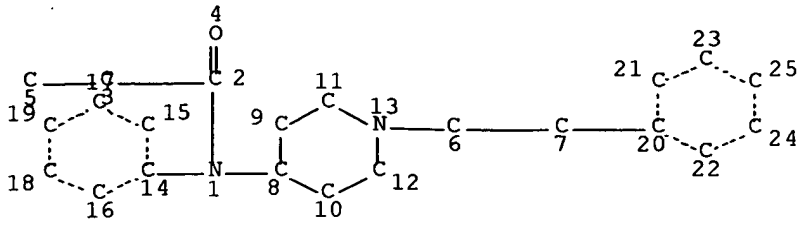
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L15          70 SEA FILE=REGISTRY FAM FUL L13
L16          31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19          36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20          13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L26        4354 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L22
L27         490 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L23
L31       70356 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  REVERS?/BI (W) PHASE#/BI
L36        4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L26 OR L27)
L48      187446 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L51      859647 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PURIF?/BI
L52     1536035 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEPARAT?/BI
L55      195334 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HPLC/BI
L61          64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 (L) PREP/RL
L66             TRANSFER  PLU=ON  L61 1- PN :      55 TERMS
L67          12 SEA FILE=USPATFULL ABB=ON  PLU=ON  L66
L68             TRANSFER  PLU=ON  L61 1- AP :      49 TERMS
L69          13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L68
L70          13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L67 OR L69
L71           2 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L48
L72           7 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L55
L73           5 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L31
L74           7 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L71 OR L72 OR L73)
L75           8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L51
L76           8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L52
L77           9 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L74 OR L75 OR L76)
L78           6 SEA FILE=USPATFULL ABB=ON  PLU=ON  L77 AND (L22 OR L23)
L79        4705 SEA FILE=USPATFULL ABB=ON  PLU=ON  FENTANYL
L80           9 SEA FILE=USPATFULL ABB=ON  PLU=ON  L77 AND L79
L91         121 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI E/AU
L92           4 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ANTONINI EN?/AU
L102          9 SEA FILE=USPATFULL ABB=ON  PLU=ON  L71 OR L72 OR L73 OR L75 OR
                L76 OR L78 OR L80
L103          1 SEA FILE=USPATFULL ABB=ON  PLU=ON  L102 AND (L91 OR L92)


=> d stat que L104
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13             STR
```



```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L15           70 SEA FILE=REGISTRY FAM FUL L13
L16           31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18            4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19           36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22           15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23           21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L26         4354 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L22
L27          490 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L23
L31        70356 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  REVERS?/BI (W) PHASE#/BI
L36         4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L26 OR L27)
L48       187446 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L51       859647 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PURIF?/BI
L52      1536035 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEPARAT?/BI
L55       195334 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HPLC/BI
L61           64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 (L) PREP/RL
L66              TRANSFER  PLU=ON  L61 1- PN :      55 TERMS
L67           12 SEA FILE=USPATFULL ABB=ON  PLU=ON  L66
L68              TRANSFER  PLU=ON  L61 1- AP :      49 TERMS
L69           13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L68
L70           13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L67 OR L69
L71            2 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L48
L72            7 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L55
L73            5 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L31
L74            7 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L71 OR L72 OR L73)
L75            8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L51
L76            8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L52
L77            9 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L74 OR L75 OR L76)
L78            6 SEA FILE=USPATFULL ABB=ON  PLU=ON  L77 AND (L22 OR L23)
L79         4705 SEA FILE=USPATFULL ABB=ON  PLU=ON  FENTANYL
L80            9 SEA FILE=USPATFULL ABB=ON  PLU=ON  L77 AND L79
L102           9 SEA FILE=USPATFULL ABB=ON  PLU=ON  L71 OR L72 OR L73 OR L75 OR
                 L76 OR L78 OR L80
L104           1 SEA FILE=USPATFULL ABB=ON  PLU=ON  L102 AND ANTONINI?/AU


=> s L103 or L104
L107           1 L103 OR L104
```

```
=> file stnguide
FILE 'STNGUIDE' ENTERED AT 12:07:41 ON 28 DEC 2007
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=> dup rem L106 L105 L107
FILE 'ZCAPLUS' ENTERED AT 12:07:51 ON 28 DEC 2007
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FILE 'USPATFULL' ENTERED AT 12:07:51 ON 28 DEC 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L106
PROCESSING COMPLETED FOR L105
PROCESSING COMPLETED FOR L107
L108           5 DUP REM L106 L105 L107 (1 DUPLICATE REMOVED)
                 ANSWERS '1-4' FROM FILE ZCAPLUS
                 ANSWER '5' FROM FILE USPATFULL

=> d ibib abs hitind hitstr L108 1-4; d ibib abs kwic hitstr L108 5

L108 ANSWER 1 OF 5  ZCAPLUS  COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:429397  ZCAPLUS  Full-text
DOCUMENT NUMBER:          142:465755
TITLE:                    Industrial method for separation and purification of
                          fentanyl by reverse-phase
                          preparative chromatography
INVENTOR(S):              Antonini, Enrico A.
PATENT ASSIGNEE(S):       Mallinckrodt Inc., USA
SOURCE:                   PCT Int. Appl., 18 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
     ----------------    ----   --------    --------------------     --------
     WO 2005044798        A1    20050519    WO 2004-US35386          20041022
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     AU 2004287815        A1    20050519    AU 2004-287815           20041022
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CA 2544195	A1	20050519	CA 2004-2544195		20041022
EP 1682505	A1	20060726	EP 2004-796374		20041022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK					
CN 1874999	A	20061206	CN 2004-80032172		20041022
JP 2007509945	T	20070419	JP 2006-538157		20041022
US 2007123710	A1	20070531	US 2006-574545		20060405
MX 2006PA04711	A	20060720	MX 2006-PA4711		20060427
IN 2006CN01440	A	20070706	IN 2006-CN1440		20060427
PRIORITY APPLN. INFO.:			US 2003-515274P	P	20031029
			WO 2004-US35386	W	20041022

AB A process for the purification of an impure preparation containing fentanyl by means of a ***reverse-phase*** preparative chromatog. process is described in which a chromatog. column is loaded with a stationary phase, typically a silica particle having an organic ligand bound thereto. With a loading ratio of from about 50-150, the impure preparation is acidified and passed through the column. The column is eluted with typically an aqueous solution of acetonitrile and the purified fentanyl is obtained in a specified cut.

IC ICM C07D211-58
ICS B01D015-08

CC 48-1 (Unit Operations and Processes)
Section cross-reference(s): 27, 45, 63

ST fentanyl purifn ***reverse phase HPLC***

IT Acids, preparation
RL: IMF (Industrial manufacture); PUR (Purification or recovery); PREP (Preparation)
(fentanyl salts; industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog. with acid salification via neutralization)

IT ***Reversed phase HPLC*** stationary phases
(in an industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog.)

IT ***Reversed phase HPLC***
(industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog.)

IT Neutralization
(industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog. with acid salification via)

IT Alcohols, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvents; in an industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog.)

IT 50-21-5, Lactic acid, reactions 110-15-6, Succinic acid, reactions 144-62-7, Oxalic acid, reactions 7664-38-2, Phosphoric acid, reactions 7664-93-9, Sulfuric acid, reactions 13598-36-2, Phosphorous acid, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(in an industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog.)

IT ***1443-54-5P***, Fentanyl hydrochloride
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog.)

IT ***437-38-7P***, Fentanyl
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); RCT (Reactant); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)

(industrial method for separation and purification of fentanyl by ***reverse -phase*** preparative chromatog.)

IT 64-18-6, Formic acid, reactions 64-19-7, Acetic acid, reactions 87-69-4, Tartaric acid, reactions 7647-01-0, Hydrochloric acid, reactions 7697-37-2, Nitric acid, reactions 10035-10-6, Hydrogen bromide, reactions
RL: RCT (Reactant); RGT (Reagent); RACT (Reactant or reagent)
(industrial method for separation and purification of fentanyl by ***reverse -phase*** preparative chromatog.)

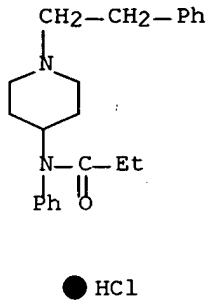
IT 75-05-8, Acetonitrile, uses 75-65-0, tert-Butanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; industrial method for separation and purification of fentanyl by ***reverse-phase*** preparative chromatog.)

IT 7631-86-9D, Silica, silanized products
RL: NUU (Other use, unclassified); USES (Uses)
(stationary phase; in an industrial method for separation and purification of
fentanyl by ***reverse-phase*** preparative chromatog.)

IT ***1443-54-5P***, Fentanyl hydrochloride
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(industrial method for separation and purification of fentanyl by ***reverse -phase*** preparative chromatog.)

RN 1443-54-5 ZCAPLUS

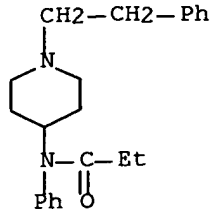
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, hydrochloride (1:1) (CA INDEX NAME)



IT ***437-38-7P***, Fentanyl
RL: PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); RCT (Reactant); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(industrial method for separation and purification of fentanyl by ***reverse -phase*** preparative chromatog.)

RN 437-38-7 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 2 OF 5 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1338171 ZCAPLUS Full-text
DOCUMENT NUMBER: 146:68877
TITLE: Method for separation and purification of naltrexone by preparative chromatography
INVENTOR(S): ***Antonini, Enrico A.***
PATENT ASSIGNEE(S): Mallinckrodt Inc., USA
SOURCE: PCT Int. Appl., 17pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006135650	A1	20061221	WO 2006-US22196	20060607

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-688956P P 20050609

AB A process for the purification of an impure preparation containing naltrexone containing 2,2-bis-naltrexone (2BN) and N-(3-butenyl)noroxymorphone (3BN) by means of a ***reverse-phase*** preparative chromatog. process is provided. In an illustrative embodiment a chromatog. column is loaded with a stationary phase, typically a silica particle having an organic ligand bound thereto. With a loading ratio of about 10 to 1000 the impure preparation is acidified and passed through the column. The column is eluted with typically an aqueous solution with acetonitrile and the purified naltrexone is obtained in a specified fraction.

CC 63-8 (Pharmaceuticals)
ST naltrexone purifn preparative ***liq chromatog***
IT Esters, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(aliphatic, stationary phase containing; separation and purification of naltrexone by

reverse-phase preparative ***liquid*** ***chromatog.***)

IT Sulfonic acids, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(alkanesulfonic, stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liq*** . ***chromatog.***)

IT Silanes
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(alkyl, stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid*** ***chromatog.***)

IT Sulfonic acids, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(arenesulfonic, stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liq*** . ***chromatog.***)

IT Carboxylic acids, analysis
Esters, analysis
Ethers, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(aromatic, stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid*** ***chromatog.***)

IT Silanes
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(aryl, stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid*** ***chromatog.***)

IT Organic compounds, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(cyano, stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid*** ***chromatog.***)

IT Ethers, analysis
Silanes
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(haloalkyl, stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid*** ***chromatog.***)

IT Acids, uses
RL: NUU (Other use, unclassified); USES (Uses)
(inorg., mobile phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid*** ***chromatog.***)

IT Acids, uses
RL: NUU (Other use, unclassified); USES (Uses)
(organic, mobile phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid*** ***chromatog.***)

IT Solvents
(organic; separation and purification of naltrexone by ***reverse-***

phase preparative ***liquid chromatog.***)

IT Preparative ***liquid chromatography***
Reversed phase liquid chromatography
(separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT Polyamides, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT Carboxylic acids, analysis
RL: ARU (Analytical role, unclassified); NUU (Other use, unclassified); ANST (Analytical study); USES (Uses)
(stationary and mobile phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT Amines, analysis
Ethers, analysis
Glycols, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT 50-21-5, Lactic acid, uses 64-18-6, Formic acid, uses 64-19-7, Acetic acid, uses 87-69-4, Tartaric acid, uses 144-62-7, Oxalic acid, uses 6915-15-7, Malic acid 7647-01-0, Hydrochloric acid, uses 7664-38-2, Phosphoric acid, uses 7664-93-9, Sulfuric acid, uses 7697-37-2, Nitric acid, uses 10035-10-6, Hydrobromic acid, uses 13598-36-2, Phosphorous acid, uses
RL: NUU (Other use, unclassified); USES (Uses)
(mobile phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 71-23-8, n-Propanol, uses 71-36-3, n-Butanol, uses 75-05-8, Acetonitrile, uses 75-65-0, tert-Butanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT 16590-41-3P, Naltrexone 16676-29-2P, Naltrexone hydrochloride
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT 189016-90-8 607732-61-6
RL: REM (Removal or disposal); PROC (Process)
(separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

IT 9003-70-7, Polystyrenedivinylbenzene 18623-11-5, Octadecylsilane 20526-39-0 25038-54-4D, Polycaprolactam, amino derivs.
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(stationary phase containing; separation and purification of naltrexone by ***reverse-phase*** preparative ***liquid chromatog.***)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 3 OF 5 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:469453 ZCAPLUS Full-text
DOCUMENT NUMBER: 144:468350

TITLE: Method for separation and purification of hydrocodone by preparative chromatography
INVENTOR(S): ***Antonini, Enrico A.***
PATENT ASSIGNEE(S): Mallinckrodt Inc., USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006052456	A1	20060518	WO 2005-US38603	20051026
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005305236	A1	20060518	AU 2005-305236	20051026
CA 2585533	A1	20060518	CA 2005-2585533	20051026
EP 1807433	A1	20070718	EP 2005-820862	20051026
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN 101065384	A	20071031	CN 2005-80040898	20051026
US 2007293676	A1	20071220	US 2007-576059	20070327
IN 2007CN01751	A	20070831	IN 2007-CN1751	20070427
PRIORITY APPLN. INFO.:			US 2004-622430P P	20041027
			WO 2005-US38603 W	20051026

AB A process for the purification of an impure preparation containing hydrocodone by means of a ***reverse phase*** preparative chromatog. process is provided. In an illustrative embodiment a chromatog. column is loaded with a stationary phase, typically a silica particle having an organic ligand bound thereto. The impure preparation is acidified and passed through the column with a loading ratio of from about 10 to about 1000. The column is eluted, typically with an aqueous solution of acetonitrile, and the purified hydrocodone is obtained in a specified fraction.

CC 31-3 (Alkaloids)
Section cross-reference(s): 63
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L108 ANSWER 4 OF 5 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:719484 ZCAPLUS Full-text
DOCUMENT NUMBER: 139:247494
TITLE: Method and system for separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatography
INVENTOR(S): ***Antonini, Enrico A.***
PATENT ASSIGNEE(S): Mallinckrodt Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003074526	A2	20030912	WO 2003-US4498		20030218
WO 2003074526	A3	20031204			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2477739	A1	20030912	CA 2003-2477739		20030218
AU 2003216279	A1	20030916	AU 2003-216279		20030218
EP 1487838	A2	20041222	EP 2003-743676		20030218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
CN 1639166	A	20050713	CN 2003-804869		20030218
JP 2005522460	T	20050728	JP 2003-572994		20030218
US 2005182257	A1	20050818	US 2004-501353		20040714
MX 2004PA08213	A	20050516	MX 2004-PA8213		20040824
IN 2004CN01890	A	20070720	IN 2004-CN1890		20040825
ZA 200405932	A	20060531	ZA 2004-5932		20060316
PRIORITY APPLN. INFO.:			US 2002-360321P	P	20020228
			US 2002-434597P	P	20021216
			WO 2003-US4498	W	20030218

AB Narcotic alkaloids are separated by feeding a crude alkaloids solution into a chromatog. column containing a compressed ***reversed-phase*** stationary phase, applying an acidic solution (pH 2-5) to the chromatog. column to recover eluates containing morphine, codeine, oripavine, papaverine, thebaine, and narcotine, resp. from the chromatog. column, adding a caustic solution to resp. eluate to precipitate and sep. the alkaloid. The mobile phase can be acetonitrile, water, ethanol, and iso-propanol. The stationary phase can consist of chemical modified silica, titania, zirconia, or a polymer. The acidic solution can contain acetic acid, formic acid, oxalic acid, succinic acid, lactic acid, and tartaric acid. A reagent can be added to the crude alkaloid solution, such as triethylamine, tetrabutylammonium hydrogen sulfate, sodium dodecyl sulfate, sodium heptane sulfonate, or ammonium sulfate. The caustic solution can contain NaOH, KOH, NH4OH, and carbonate salts of alkali metals. A system for separating at least one narcotic alkaloid consists of a chromatog. column having a fluid chamber and a media chamber, with a diameter of ≥ 5 cm having an inlet connected to a liquid tank via a 1st valve, an outlet connected to an eluate tank via a 2nd valve, and a fluid purge orifice connected to the outlet via a 3rd valve, a double-acting piston that includes a plate, having an upper face and a lower face, and a rod. The piston is located within the chromatog. column for compressing the stationary phase between the lower face of the plate and the bottom of the chromatog. column. A hydraulic pump provides fluid to the double-acting piston.

IC ICM C07D489-02
CC 48-1 (Unit Operations and Processes)
Section cross-reference(s): 31
ST narcotic alkaloid sepn ***reversed phase*** preparative column chromatog
IT Narcotics

Papaver
Preparative ***liquid chromatography***
Reversed phase chromatographic stationary phases
(separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatog.)

IT Alkaloids, preparation
RL: PUR (Purification or recovery); PREP (Preparation)
(separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatog.)

IT Carbonates, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatog.)

IT 64-17-5, Ethanol, uses 67-63-0, Iso-propanol, uses 75-05-8, Acetonitrile, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(mobile phase; separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatog.)

IT 57-27-2P, Morphine, preparation 58-74-2P, Papaverine 76-57-3P, Codeine 115-37-7P, Thebaine 128-62-1P, Narcotine 467-04-9P, Oripavine 597541-62-3P
RL: PUR (Purification or recovery); PREP (Preparation)
(separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatog.)

IT 50-21-5, Lactic acid, reactions 64-18-6, Formic acid, reactions 64-19-7, Acetic acid, reactions 87-69-4, Tartaric acid, reactions 110-15-6, Butanedioic acid, reactions 121-44-8, Triethylamine, reactions 144-62-7, Ethanedioic acid, reactions 151-21-3, Sodium dodecyl sulfate, reactions 1310-58-3, Potassium hydroxide (KOH), reactions 1310-73-2, Sodium hydroxide (NaOH), reactions 1336-21-6, Ammonium hydroxide ((NH4)(OH)) 7783-20-2, Ammonium sulfate, reactions 22767-50-6, Sodium heptane sulfonate 32503-27-8, Tetrabutylammonium hydrogen sulfate
RL: RCT (Reactant); RACT (Reactant or reagent)
(separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatog.)

IT 1314-23-4D, Zirconia, derivs. 7631-86-9D, Silica, derivs. 13463-67-7D, Titania, derivs.
RL: NUU (Other use, unclassified); USES (Uses)
(stationary phase; separation and purification of narcotic alkaloids using ***reversed-phase*** preparative chromatog.)

L108 ANSWER 5 OF 5 USPATFULL on STN

ACCESSION NUMBER:	2007:141719 USPATFULL Full-text			
TITLE:	Industrial method for seperation and ***purification*** of ***fentanyl*** by ***reverse phase*** preparative chromatography			
INVENTOR(S):	***Antonini, Enrico Anthony***, Edwardsville, IL, UNITED STATES			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2007123710	A1	20070531	<--
APPLICATION INFO.:	US 2004-574545	A1	20041022	(10)
	WO 2004-US35386		20041022	
			20060405	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-515274P	20031029 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Jeffrey S Boone, Mallinckrodt Inc, 675 McDonnell Boulevard, PO Box 5840, St Louis, MO, 63134, US	
NUMBER OF CLAIMS:	25	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	1 Drawing Page(s)	
LINE COUNT:	539	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There is described a process for the ***purification*** of an impure preparation containing ***fentanyl*** by means of a ***reverse phase*** preparative chromatography process. A chromatographic column is loaded with a stationary phase, typically a silica particle having an organic ligand bound thereto. With a loading ratio of from about 50 to about 150 the impure preparation is acidified and passed through the column. The column is eluted with typically an aqueous solution of acetonitrile and the ***purified fentanyl*** is obtained in a specified cut.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Industrial method for seperation and ***purification*** of ***fentanyl*** by ***reverse phase*** preparative chromatography

IN ***Antonini, Enrico Anthony***, Edwardsville, IL, UNITED STATES

AI US 2004-574545 A1 20041022 (10)
20041022
20060405 PCT 371 date

AB There is described a process for the ***purification*** of an impure preparation containing ***fentanyl*** by means of a ***reverse phase*** preparative chromatography process. A chromatographic column is loaded with a stationary phase, typically a silica particle having an organic ligand. . . is acidified and passed through the column. The column is eluted with typically an aqueous solution of acetonitrile and the ***purified fentanyl*** is obtained in a specified cut.

SUMM This invention relates to a method for the ***separation*** and ***purification*** of ***fentanyl*** on an industrial scale by means of ***reverse phase*** preparative chromatography. More particularly, the process of this invention provides highly pure ***fentanyl*** conveniently and in industrial quantities.

SUMM ***Fentanyl*** is the common name for N-Phenyl-N-[1-(2phenylethyl)-4-piperidinyl]propanamide, a well-known powerful analgesic in the narcotic range and a known tranquilizer in veterinary. . .

SUMM An early process for the manufacture of ***fentanyl*** is found in U.S. Pat. No. 3,164,600 to Janssen. Following this early disclosure, precipitation and re-crystallization typically ***purified*** the product. Multiple precipitations were typically required to provide adequate purity for pharmaceutical use. In addition to yield loss in. .

SUMM One example of an attempt to improve the precipitation and crystallization process for pharmaceuticals such as ***fentanyl*** is disclosed in U.S. Pat. No. 6,596,206 to Lee. In this method a device for generating pharmaceutical agent particles using. . . still involves solvents, antisolvents and specialized equipment, all of which maintains the above noted disadvantages of the precipitation method for ***separating*** and ***purifying*** the pharmaceutical.

SUMM Other means to achieve ***separation*** or ***purification*** of pharmaceuticals includes adsorption processes such as the use of

carbon. Another is the use of adsorption through ion exchange.. . . the need for the use of high pH flushes that can cause precipitation. Any precipitation can potentially compromise the entire ***purification*** process. Another disadvantage to this process is that significant salt is required so that another step of either dialysis or. . .

SUMM . . . adsorption Although this method is successful, it requires the extensive use of organic solvents. Moreover, although the alkaloids can be ***separated*** from each other, more evaporation is required.

SUMM Any use of analytical chromatography on narcotics such as ***fentanyl*** would guide an individual of ordinary skill in the art away from using preparative chromatography for an industrial scale process. Unlike preparative chromatography, analytical chromatography generally requires complete ***separation*** of each peak. Unlike preparative chromatography, complete ***separation*** of each peak is measured by ultraviolet (UV) absorbency. This is achieved by loading an infinitely small mass of the. . . as the impurities are within specification limits. The particle size of the stationary phase is small enough to achieve the ***separation***, but is often greater than 10 microns (393.70 microinches). This limits the pressure drop generated. Also, in preparative chromatography, the. . .

SUMM Various patents refer to preparative chromatography for the purpose of ***purifying*** or ***separating*** various non-ionic chemicals. Early patents in this field are U.S. Pat. No. 4,396,598 to Lin (X-ray contrast agents) and U.S.. . .

SUMM Numerous publications followed the above '005 patent indicating various chromatographic systems, including flash, ***HPLC*** and preparative chromatography for ***separating*** various agents but not indicating conditions, clearly not teaching any industrial process. Such publications include Published Appln. US 2003/0087306, employing various chromatographic processes for ***separation*** of multimeric agents that modulate receptors, U.S. Pat. No. 6,395,752 and 6,127,385 indicating isomerization of L-threo-methylphenidate, U.S. Pat. No. 4,909,941. . .

SUMM A reference to preparative, ***reverse phase*** chromatography including a loading ratio is U.S. Pat. No. 4,317,903 disclosing the ***purification*** of lincomycin hydrochloride indicating a loading weight ratio of 18 to 1, of bonded phase silica gel to starting material. A combination of chromatographic ***separation*** followed by nanofiltration with final discoloration by ion exchange resins is described in U.S. Pat. No. 5,811,581. The material being ***separated*** in the '581 patent is described as non-ionic, water-soluble, tri- and hexa-iodinated opacifying agents useful as contrast agents in X-ray. . .

SUMM As can be seen by the above review of the prior art, numerous organic materials have been ***separated*** or ***purified*** by means of the chromatographic process. However, in most instances the conditions under which the chromatographic ***separation*** was carried out was not indicated. Also, the materials ***separated*** by means of the chromatographic processes are greatly dissimilar to the present objects of this invention, i.e. the industrial scale ***separation*** and ***purification*** of ***fentanyl***. While there are numerous references to analytical chromatographic applications for ***fentanyl***, there is no suggestion that an industrial process could be employed under any conditions.

SUMM The current process for the ***purification*** of ***fentanyl*** utilizes two crystallizations of the hydrochloride salt and one alkaloid precipitation to attain the desired purity. While the purity requirements are attained, the recovery is low as about half of the ***fentanyl*** is lost to the mother liquor streams generated due to

the solubility of the hydrochloride salt. Recycling the ***fentanyl*** in these streams is difficult due to the elevated level of impurities. There is a need for a more efficient and direct method to isolate highly pure ***fentanyl***.

SUMM ***Fentanyl*** is currently produced through a reaction using phenethylpiperaniline (PPA). The ***fentanyl*** produced precipitates away from the reaction liquor. The solids are then dissolved with water and enough hydrochloric acid is added. . .

SUMM In accordance with this invention there is provided an industrial process for recovering highly pure ***fentanyl*** from an impure, acidic, aqueous solution of ***fentanyl*** which comprises subjecting said impure ***fentanyl*** to ***reverse-phase*** preparative ***liquid chromatography***. The chromatographic process employs a packed column containing media that have a bonded-phase attached. Through a series of collected fractions, partially recycled, the highly ***purified fentanyl*** is eluted from the column and recovered in highly yield. ***Fentanyl*** is produced in accordance with this invention with PPA impurity levels less than 0.010 weight percent in the ***purified*** product.

DRWD The attached FIGURE is a graph indicating the results of a ***reverse phase***, preparative ***HPLC*** procedure in accordance with this invention wherein the UV analysis of the product provides an indication of the contents of. . .

DETD Loading ratio: Mass of stationary phase divided by the mass of alkaloid loaded in ***purification*** runs.

DETD . . . alkaloid mass recovered in fractions that require a second pass through the chromatography column. The fractions are concentrated and then ***purified separately***.

DETD Yield: The mass of desired component recovered in ***purified*** fractions divided by the mass of component fed to the column.

DETD In accordance this invention, ***fentanyl*** is obtained through a reaction using phenethylpiperaniline. As noted above the precipitate from that reaction is used to prepare the. . . is first dissolved in water and the solution is acidified with an appropriate acidifying agent. Typically, the concentration of the ***fentanyl*** in the aqueous solution is in the range of from about 5 g/l to about 35 g/l and conveniently about 20 g/l. Non-limiting examples of an acids employed to acidify the ***fentanyl*** solution include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, phosphorous acid, nitric. . . acid and tartaric acid. The amount of acid employed is that which is sufficient to lower the pH of the ***fentanyl*** solution to a pH that is preferably in a range from about 2 to about 5 and most preferably a. . . about 4. A dilute inorganic acid such as dilute hydrochloric acid is preferred since other stronger acids may degrade the ***fentanyl*** solution. The amount of acid added is to ensure that the ***fentanyl*** is converted to a salt. It has been found that the maximum retention of ***fentanyl*** is obtained when the ***fentanyl*** is fed to the column in the free base form. Thus, to ensure that the ***fentanyl*** can be recovered in a reasonable flush volume, the feed solution needs to be properly acidified. A solution containing from about 0.5 percent to about 3.5 percent ***fentanyl*** is typically prepared. Preferred solutions contain from about 1.5 to about 2.5 percent ***fentanyl*** and most preferred solutions contain about 2.0 percent ***fentanyl***.

DETD A high-performance preparative ***liquid chromatography*** column is generally employed. The preparative chromatography column, in an exemplary preferred system, includes a diameter that is at least. .

DETD ***Fentanyl*** and impurities are adsorbed onto the stationary phase and are desorbed, or eluted with a mobile phase containing dilute

hydrochloric. . .

DETD . . . this invention is typically in the range of from about 50 to about 150 grams of media per gram of ***fentanyl*** loaded into the column before the mobile phase is employed. Most typically, the Loading Ratio is in the range of from about 70 to about 130. As is well known, in the analytical use of ***HPLC*** the Loading Ratio would be above 10,000 and the feed components would elute in ***separate*** peaks. In the preparative chromatography such Loading Ratio would multiply the number of runs in a column by a factor. . . the column to have more than 10 times larger diameter. Using the analytical loading conditions would make any new chromatography ***purification*** technique impractical. The feasible preparative application has elution fronts, in which the ***fentanyl*** is collected with the desired purity.

DETD In operation, after the ***fentanyl*** feed solution is loaded into the packed column, the first components are eluted with a mobile phase containing from about. . . are collected in a first fraction and is discarded. A second fraction is collected containing an initial, small amount of ***fentanyl*** and the remaining PPA. The second crop will contain about 10 percent of the ***fentanyl*** loaded. The ***purified fentanyl*** is then collected in the third fraction wherein the mobile phase is changed to an increased amount of solvent, in. . . in the third fraction can be as high as 15 percent. The third fraction contains about 90 percent of the ***fentanyl*** loaded into the column. This third fraction is evaporated to remove the solvent and the ***purified*** alkaloid is recovered from solution by precipitation in accordance with standard procedures. A fourth fraction is then obtained to flush the column of the remaining ***fentanyl*** loaded. In the fourth fraction, the aqueous mobile phase employed contains about 50 percent organic solvent, typically acetonitrile. This fourth. . . the second fraction and subjected to evaporation to remove the organic solvent. The combined fractions are subjected to the preparative, ***reverse phase*** preparative chromatography as described above except that no recycle fractions are collected in order to purge the impurities. The ***purified***, combined second crop is then sent to the alkaloid precipitation procedure as noted above with respect to the third fraction.

DETD The ***reverse phase***, preparative chromatographic process of this invention is typically operated at a temperature of from about 20° C. to about 30°. . .

DETD . . . this invention appears in the Figure. The process producing the UV curve in the Figure employed a feed solution of ***fentanyl*** hydrochloride salt at pH 3.0 to a chromatographic column having a dimension of 1+25-cm, with 15/30-micron particles of silicon having. . .

DETD A series of runs were performed to demonstrate the recovery and purity attained with the preparative, ***reverse phase***, preparative chromatography ***purification*** of ***fentanyl***. All runs used a column packed with 20-micron silica containing C8 ligands and providing 120 angstroms pores. The mobile phase. . . 2.8-3.2 with increasing acetonitrile. The results obtained in these runs are set forth in Table I below

TABLE I

			Purified Fentanyl Fraction					
	Second Fraction							
Run	Load Ratio	Area %	% Yield	g/l Fent.	PPA %	% ACN	Area % PPA %	%. . .

DETD Objective: Recover ***fentanyl*** with less than 0.010 percent PPA

DETD Feed Composition: 91.2 area % ***fentanyl***, 8.6 area % (0.91 weight %) PPA

DETD Feed concentration: 19-g/l ***fentanyl***

DETD . . . of the two runs appear in Table II below.

TABLE II

	RUN 1	RUN 2
Loading Ratio	103	50
Area % ***fentanyl*** in ***purified*** fraction	99.88	98.48
Percent PPA in ***purified*** fraction	0.006	0.029
Yield of ***fentanyl*** in ***purified*** fraction	87	86
Elution prior to ***fentanyl*** elution	27.3 ml of aqueous 66.5 ml of 2.5% ACN	69 ml of aqueous 45 ml of 5% ACN
Elution of ***fentanyl***-PPA fraction	5.3 ml of 2.5% ACN	10.8 ml of 5% ACN
Elution of ***purified*** fraction	27.5 ml of 2.5% ACN 34.0 ml of 15% ACN	26.7 ml of 5% ACN 40.5 ml of 10% ACN 44.5 ml of 15% ACN
Elution of late-eluting ***fentanyl*** fraction	22.1 ml of 15% ACN 32.5 ml of 50% ACN 11 ml of 100% ACN	28.5 ml of 50% ACN 15 ml of 95% ACN

DETD . . . loading ratio of 103 while Run 2 of Table 2 loaded too much feed at a ratio of 50. The ***separation*** of ***fentanyl*** and PPA was aided in Run 1 by using an initial acetonitrile flush of 2.5 volume percent. Run 2 used a higher initial acetonitrile flush of 5 volume percent and this made ***separating*** the PPA and ***fentanyl*** more difficult. Both runs had nearly the same recovery of ***fentanyl*** in the ***purified*** fraction, and the remaining ***fentanyl*** was recovered in the ***fentanyl***-PPA and late-eluting fractions. These fractions were designated as second crop and were to be ***purified*** a second time through the column.

DETD . . . the runs are contained in Table III below.

TABLE III

	RUN 3	RUN 4
Loading Ratio	88	64
Area % of ***fentanyl*** in ***purified*** fraction	99.89	98.65
Weight % of PPA in ***purified*** fraction	0.007	0.014
Yield of ***fentanyl*** in ***purified*** fraction	91	86
Elution prior to ***fentanyl*** elution	27.5 ml of aqueous 45.0 ml of 5% ACN	31 ml of aqueous 71.8 ml of 5% ACN
Elution of ***fentanyl***-PPA fraction	8.6 ml 5% ACN	6.7 ml of 5% ACN
Elution of ***purified*** fraction	36.2 ml of 5% ACN 31.0 ml of 15% ACN	24.1 ml of 5% ACN 38.5 ml of 10% ACN 49.0 ml of 15% ACN
Elution of late-eluting ***fentanyl*** fraction	27 ml of 15% ACN 36.5 ml of 50% ACN	39.5 ml of 50% ACN

9.0 ml of 100% ACN

DETD . . . of 64 compared to 88 for Run 3. Run 3 used less elution volume than Run 4 to collect the ***purified fentanyl***. This was because Run 3 omitted the flush of 10% acetonitrile. It is clear from the data in Table III. . . . of impurity in the feed as well as to compensate for other operating conditions. The use of a slightly larger ***fentanyl***-PPA fraction volume in Run 3 also aided in the reduction of PPA.

DETD There has been described a novel process for the preparation of ***fentanyl*** by means of ***reverse phase,*** preparative chromatography. While the process of this invention has been described with reference to specific compounds and examples, no intention. . .

CLM What is claimed is:

1. An industrial process for recovering highly pure ***fentanyl*** from an impure preparation which comprises subjecting said impure preparation to a ***reverse-phase*** high performance preparative ***liquid chromatography*** and recovering highly pure ***fentanyl***.

14. The process of claim 1 wherein the impure preparation is acidified so as to prepare a ***fentanyl*** salt.

15. The process of claim 14 wherein the acid employed to acidify the aqueous solution of ***fentanyl*** is an inorganic acid.

17. The process of claim 14 wherein the acid employed to acidify the aqueous solution of ***fentanyl*** is an organic acid.

19. The process of claim 14 wherein the pH of the aqueous solution of ***fentanyl*** is in the range of from about 2 to about 5.

20. The process of claim 19 wherein the pH of the aqueous solution of ***fentanyl*** is in the range of about from about 2.5 to about 3.5.

. . . the acetonitrile is in the range of from about 5 to about 10 volume percent during the collection of the ***purified fentanyl***

.

24. The process for ***purifying*** an impure preparation of ***fentanyl*** containing phenethylpiperaniline which comprises the steps of (a) packing a chromatographic column with a chromatographic packing material; (b) passing through said column an aqueous, acidified solution of impure ***fentanyl*** at a loading ratio of from about 50 to about 150 and (c) eluting said column with an aqueous solution of an organic solvent to produce an eluate containing ***fentanyl*** having less than about 0.010 percent phenethylpiperaniline.

IT ***1443-54-5P***, Fentanyl hydrochloride
(industrial method for separation and purification of fentanyl by reverse-phase
preparative chromatog.)

IT ***437-38-7P***, Fentanyl
(industrial method for separation and purification of fentanyl by reverse-phase
preparative chromatog.)

IT ***1443-54-5P***, Fentanyl hydrochloride
(industrial method for separation and purification of fentanyl by reverse-phase
preparative chromatog.)

RN 1443-54-5 USPATFULL
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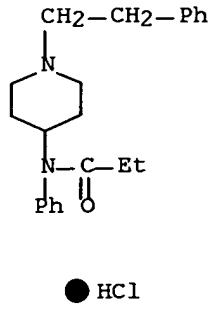

IT ***437-38-7P***, Fentanyl
(industrial method for separation and purification of fentanyl by reverse-phase
preparative chromatog.)
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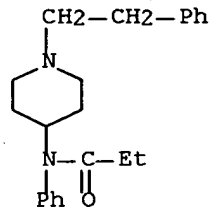

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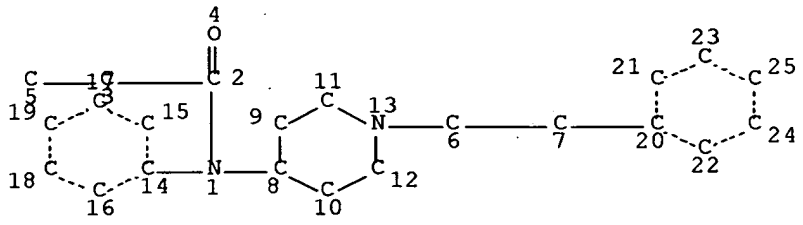

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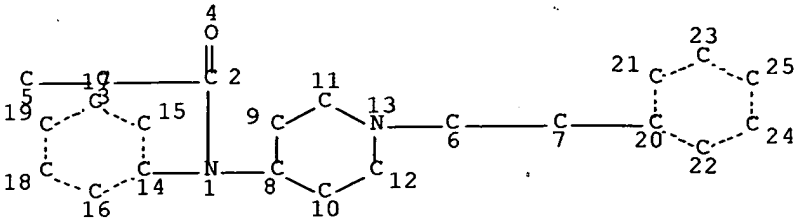

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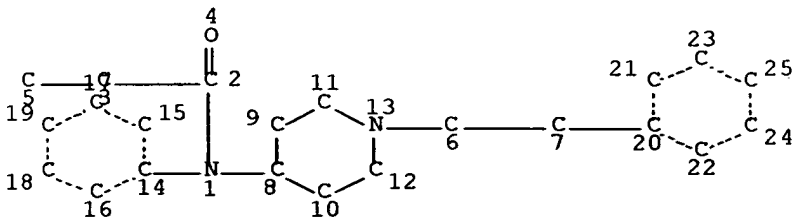

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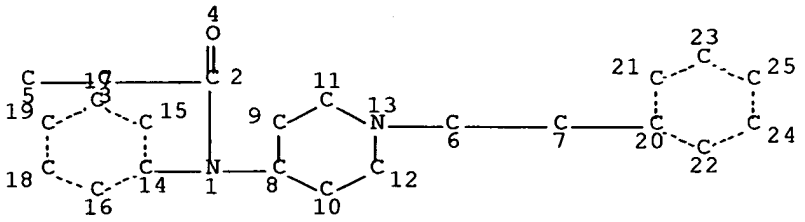

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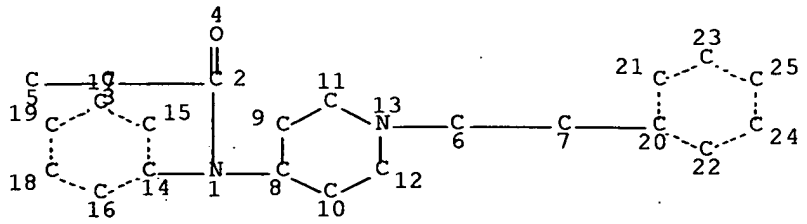

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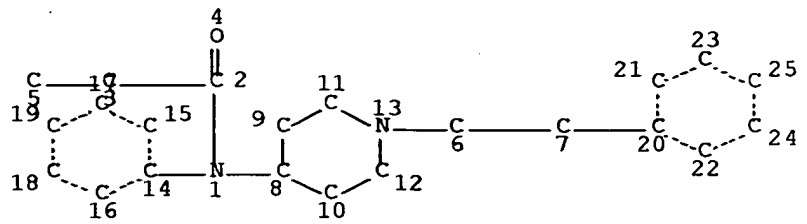
L5              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                  2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10             3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13               STR
```



```
NODE ATTRIBUTES:
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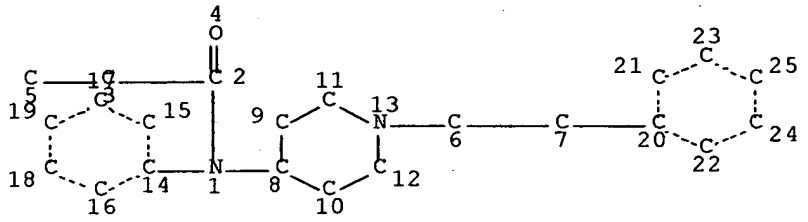
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L15           70 SEA FILE=REGISTRY FAM FUL L13
L16           31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18            4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19           36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22           15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23           21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L52      1536035 SEA FILE=HCAPLUS ABB=ON   PLU=ON  SEPARAT?/BI
L81         4765 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  (L22 OR L23)
L83            2 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  L81 (3W) L52


=> d stat que L86
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                  2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13              STR
```



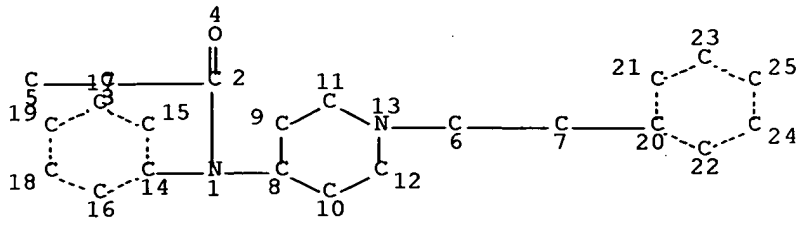
```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L15           70 SEA FILE=REGISTRY FAM FUL L13
L16           31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18            4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19           36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22           15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23           21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L29        12386 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  REVERSED PHASE HPLC/CW
L40       195334 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  HPLC/BI
L44       187446 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  ?LIQUID CHROMATOG?/BI
L52      1536035 SEA FILE=HCAPLUS ABB=ON   PLU=ON  SEPARAT?/BI
L81         4765 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  (L22 OR L23)
```

```
L84          19 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L81 (L) L52
L86           3 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L84 AND (L29 OR L40 OR L44)


=> d stat que L89
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                  2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L9       815720 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ?CHROMATOG?/BI
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L11           3 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L10 (L) PUR/RL
L12           3 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L9 AND L11
L13             STR
```



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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L15          70 SEA FILE=REGISTRY FAM FUL L13
L16          31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19          36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20          13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L26        4354 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L22
L27         490 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L23
L29       12386 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  REVERSED PHASE HPLC/CW
L30           8 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L26 AND L29
L31       70356 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  REVERS?/BI (W) PHASE#/BI
L32           3 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L27 AND L29
L36        4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L26 OR L27)
L38          64 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L36 (L) PREP/RL
L39           5 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L38 AND L9
L40      195334 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  HPLC/BI
L41           1 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L38 AND L40
L42           1 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L31 AND L38
L44      187446 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L52     1536035 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEPARAT?/BI
L81        4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L22 OR L23)
L83           2 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L81 (3W) L52
L84          19 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L81 (L) L52
L86           3 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L84 AND (L29 OR L40 OR L44)
```

```
L87          17 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L11 OR L12 OR L30 OR L32 OR
                L39 OR L41 OR L42 OR L83 OR L86
L88          17 SEA FILE=REGISTRY ABB=ON  PLU=ON  (10035-10-6/BI OR 110-15-6/BI
                 OR 13598-36-2/BI OR 144-62-7/BI OR 1443-54-5/BI OR 437-38-7/BI
                 OR 50-21-5/BI OR 64-18-6/BI OR 64-19-7/BI OR 75-05-8/BI OR
                75-65-0/BI OR 7631-86-9/BI OR 7647-01-0/BI OR 7664-38-2/BI OR
                7664-93-9/BI OR 7697-37-2/BI OR 87-69-4/BI)
L89          13 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L88 AND L87


=> s (L11 or L12 or L30 or L32 or L39  or L41 or L42 or L83 or L86 or L89) not L106
L109         16 (L11 OR L12 OR L30 OR L32 OR L39 OR L41 OR L42 OR L83 OR L86 OR
                L89) NOT L106

=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 12:10:07 ON 28 DEC 2007
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FILE COVERS 1907 - 28 Dec 2007  VOL 148 ISS 1
FILE LAST UPDATED: 27 Dec 2007  (20071227/ED)

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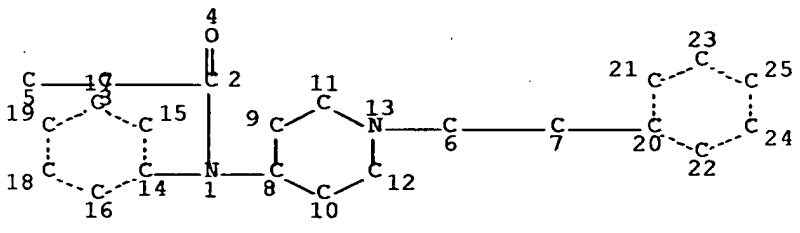
 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d stat que L53
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13             STR
```



```
NODE ATTRIBUTES:
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

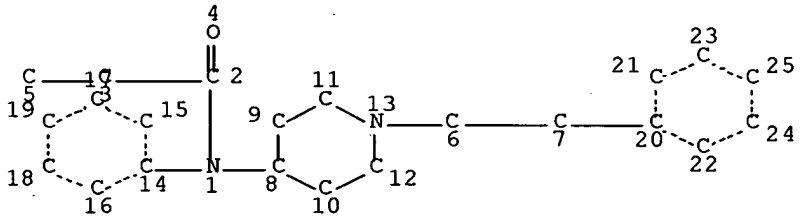
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L15	70	SEA FILE=REGISTRY FAM FUL L13	
L16	31	SEA FILE=REGISTRY ABB=ON PLU=ON	L15 AND MXS/CI
L18	4	SEA FILE=REGISTRY ABB=ON PLU=ON	L15 AND C>22
L19	36	SEA FILE=REGISTRY ABB=ON PLU=ON	L15 NOT (L16 OR L18)
L20	13	SEA FILE=REGISTRY ABB=ON PLU=ON	L19 AND NC<2
L22	15	SEA FILE=REGISTRY ABB=ON PLU=ON	L20 OR L10
L23	21	SEA FILE=REGISTRY ABB=ON PLU=ON	L19 NOT L22
L45	132461	SEA FILE=HCAPLUS ABB=ON PLU=ON	LIQUID CHROMATOGRAPHY+NT,OLD/CT
L46	4765	SEA FILE=HCAPLUS ABB=ON PLU=ON	L22 OR L23
L47	71	SEA FILE=HCAPLUS ABB=ON PLU=ON	L45 AND L46
L48	187446	SEA FILE=HCAPLUS ABB=ON PLU=ON	?LIQUID CHROMATOG?/BI
L49	100	SEA FILE=HCAPLUS ABB=ON PLU=ON	L46 AND L48
L50	113	SEA FILE=HCAPLUS ABB=ON PLU=ON	L47 OR L49
L51	859647	SEA FILE=HCAPLUS ABB=ON PLU=ON	PURIF?/BI
L53	2	SEA FILE=HCAPLUS ABB=ON PLU=ON	L50 AND L51

=> d stat que L54

L2	1	SEA FILE=REGISTRY ABB=ON PLU=ON	437-38-7
L4	1	SEA FILE=REGISTRY ABB=ON PLU=ON	1443-54-5
L5	1	SEA FILE=REGISTRY ABB=ON PLU=ON	"PROPANAMIDE, N-PHENYL-N-(1-(2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10	3	SEA FILE=REGISTRY ABB=ON PLU=ON	L2 OR L4 OR L5
L13		STR	



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

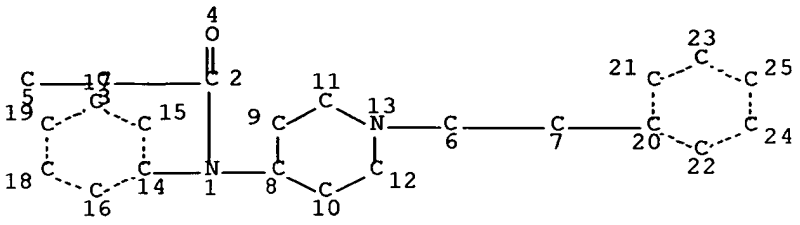
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L15	70	SEA FILE=REGISTRY FAM FUL L13	
L16	31	SEA FILE=REGISTRY ABB=ON PLU=ON	L15 AND MXS/CI
L18	4	SEA FILE=REGISTRY ABB=ON PLU=ON	L15 AND C>22
L19	36	SEA FILE=REGISTRY ABB=ON PLU=ON	L15 NOT (L16 OR L18)
L20	13	SEA FILE=REGISTRY ABB=ON PLU=ON	L19 AND NC<2
L22	15	SEA FILE=REGISTRY ABB=ON PLU=ON	L20 OR L10

```
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L45      132461 SEA FILE=HCAPLUS ABB=ON   PLU=ON  LIQUID CHROMATOGRAPHY+NT,OLD/C
                T
L46        4765 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L22 OR L23
L47          71 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L45 AND L46
L48      187446 SEA FILE=HCAPLUS ABB=ON   PLU=ON  ?LIQUID CHROMATOG?/BI
L49         100 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L46 AND L48
L50         113 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L47 OR L49
L52     1536035 SEA FILE=HCAPLUS ABB=ON   PLU=ON  SEPARAT?/BI
L54          32 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L50 AND L52


=> d stat que L58
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13             STR
```



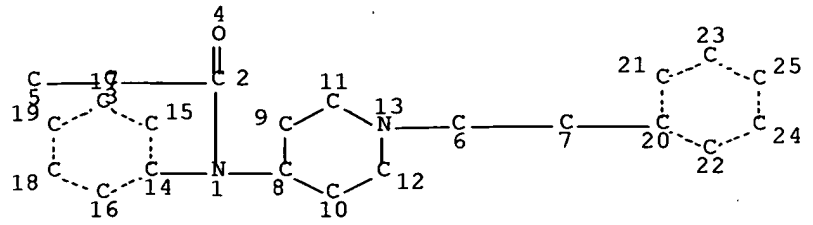
```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L15          70 SEA FILE=REGISTRY FAM FUL L13
L16          31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19          36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20          13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L46        4765 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L22 OR L23
L51      859647 SEA FILE=HCAPLUS ABB=ON   PLU=ON  PURIF?/BI
L55      195334 SEA FILE=HCAPLUS ABB=ON   PLU=ON  HPLC/BI
L57          90 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L46 AND L55
L58           4 SEA FILE=HCAPLUS ABB=ON   PLU=ON  L57 AND L51


=> d stat que L59
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
```

L13 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

```
L15          70 SEA FILE=REGISTRY FAM FUL L13
L16          31 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND MXS/CI
L18           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19          36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20          13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L46        4765 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 OR L23
L52     1536035 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEPARAT?/BI
L55      195334 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HPLC/BI
L57          90 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L46 AND L55
L59          22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L57 AND L52
```

```
=> s (L53 or L54 or L58 or L59) not L105
L110        37 (L53 OR L54 OR L58 OR L59) NOT L105

=> file uspatfull
FILE 'USPATFULL' ENTERED AT 12:10:46 ON 28 DEC 2007
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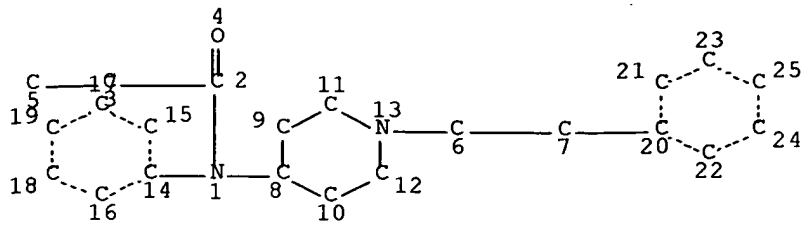
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Dec 2007 (20071227/PD)
FILE LAST UPDATED: 27 Dec 2007 (20071227/ED)
HIGHEST GRANTED PATENT NUMBER: US7313828
HIGHEST APPLICATION PUBLICATION NUMBER: US2007300346
CA INDEXING IS CURRENT THROUGH 27 Dec 2007 (20071227/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Dec 2007 (20071227/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2007
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2007

=> d stat que L71
L2            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                  2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13             STR
```



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

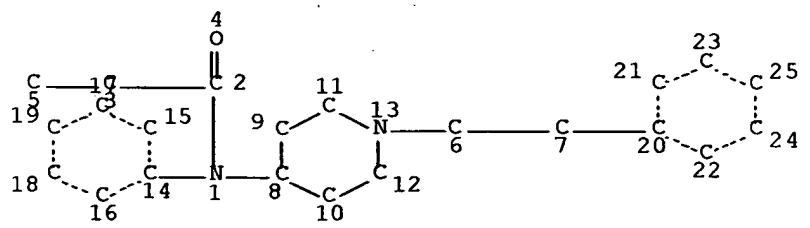
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L15	70	SEA FILE=REGISTRY FAM FUL L13
L16	31	SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND MXS/CI
L18	4	SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND C>22
L19	36	SEA FILE=REGISTRY ABB=ON PLU=ON L15 NOT (L16 OR L18)
L20	13	SEA FILE=REGISTRY ABB=ON PLU=ON L19 AND NC<2
L22	15	SEA FILE=REGISTRY ABB=ON PLU=ON L20 OR L10
L23	21	SEA FILE=REGISTRY ABB=ON PLU=ON L19 NOT L22
L26	4354	SEA FILE=ZCAPLUS ABB=ON PLU=ON L22
L27	490	SEA FILE=ZCAPLUS ABB=ON PLU=ON L23
L36	4765	SEA FILE=ZCAPLUS ABB=ON PLU=ON (L26 OR L27)
L48	187446	SEA FILE=HCAPLUS ABB=ON PLU=ON ?LIQUID CHROMATOG?/BI
L61	64	SEA FILE=HCAPLUS ABB=ON PLU=ON L36 (L) PREP/RL
L66		TRANSFER PLU=ON L61 1- PN : 55 TERMS
L67	12	SEA FILE=USPATFULL ABB=ON PLU=ON L66
L68		TRANSFER PLU=ON L61 1- AP : 49 TERMS
L69	13	SEA FILE=USPATFULL ABB=ON PLU=ON L68
L70	13	SEA FILE=USPATFULL ABB=ON PLU=ON L67 OR L69
L71	2	SEA FILE=USPATFULL ABB=ON PLU=ON L70 AND L48

=> d stat que L72

L2	1	SEA FILE=REGISTRY ABB=ON PLU=ON 437-38-7
L4	1	SEA FILE=REGISTRY ABB=ON PLU=ON 1443-54-5
L5	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PROPANAMIDE, N-PHENYL-N-(1-(2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10	3	SEA FILE=REGISTRY ABB=ON PLU=ON L2 OR L4 OR L5
L13		STR



NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

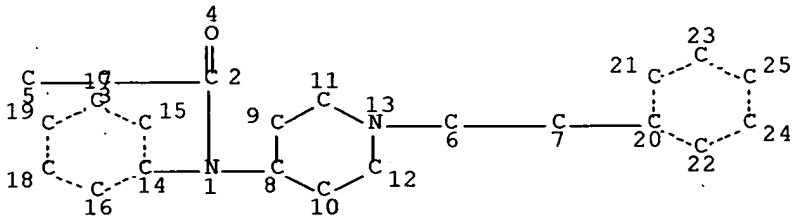
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

L15	70	SEA FILE=REGISTRY FAM FUL L13
L16	31	SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND MXS/CI
L18	4	SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND C>22
L19	36	SEA FILE=REGISTRY ABB=ON PLU=ON L15 NOT (L16 OR L18)
L20	13	SEA FILE=REGISTRY ABB=ON PLU=ON L19 AND NC<2
L22	15	SEA FILE=REGISTRY ABB=ON PLU=ON L20 OR L10
L23	21	SEA FILE=REGISTRY ABB=ON PLU=ON L19 NOT L22
L26	4354	SEA FILE=ZCAPLUS ABB=ON PLU=ON L22
L27	490	SEA FILE=ZCAPLUS ABB=ON PLU=ON L23
L36	4765	SEA FILE=ZCAPLUS ABB=ON PLU=ON (L26 OR L27)
L55	195334	SEA FILE=HCAPLUS ABB=ON PLU=ON HPLC/BI
L61	64	SEA FILE=HCAPLUS ABB=ON PLU=ON L36 (L) PREP/RL
L66		TRANSFER PLU=ON L61 1- PN : 55 TERMS
L67	12	SEA FILE=USPATFULL ABB=ON PLU=ON L66
L68		TRANSFER PLU=ON L61 1- AP : 49 TERMS
L69	13	SEA FILE=USPATFULL ABB=ON PLU=ON L68
L70	13	SEA FILE=USPATFULL ABB=ON PLU=ON L67 OR L69
L72	7	SEA FILE=USPATFULL ABB=ON PLU=ON L70 AND L55

=> d stat que L73

L2	1	SEA FILE=REGISTRY ABB=ON PLU=ON 437-38-7
L4	1	SEA FILE=REGISTRY ABB=ON PLU=ON 1443-54-5
L5	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PROPANAMIDE, N-PHENYL-N-(1-(2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10	3	SEA FILE=REGISTRY ABB=ON PLU=ON L2 OR L4 OR L5
L13		STR



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GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

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L16	31	SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND MXS/CI
L18	4	SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND C>22
L19	36	SEA FILE=REGISTRY ABB=ON PLU=ON L15 NOT (L16 OR L18)

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L20          13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L26        4354 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L22
L27         490 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L23
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L36        4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L26 OR L27)
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L67          12 SEA FILE=USPATFULL ABB=ON  PLU=ON  L66
L68             TRANSFER  PLU=ON  L61 1- AP :      49 TERMS
L69          13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L68
L70          13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L67 OR L69
L73           5 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L31


=> d stat que L75
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L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
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L10           3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13             STR
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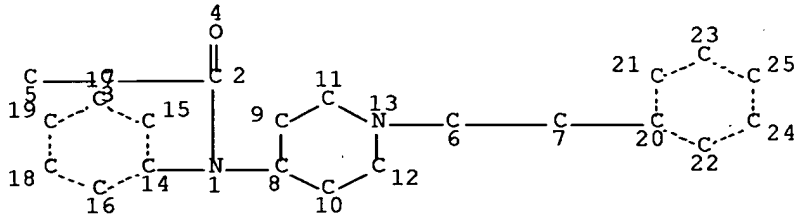

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L18           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19          36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20          13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22          15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23          21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L26        4354 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L22
L27         490 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L23
L36        4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L26 OR L27)
L51      859647 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PURIF?/BI
L61          64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 (L) PREP/RL
L66             TRANSFER  PLU=ON  L61 1- PN :      55 TERMS
L67          12 SEA FILE=USPATFULL ABB=ON  PLU=ON  L66
L68             TRANSFER  PLU=ON  L61 1- AP :      49 TERMS
L69          13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L68
```

```
L70           13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L67 OR L69
L75            8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L51


=> d stat que L76
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  437-38-7
L4             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                 2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13              STR
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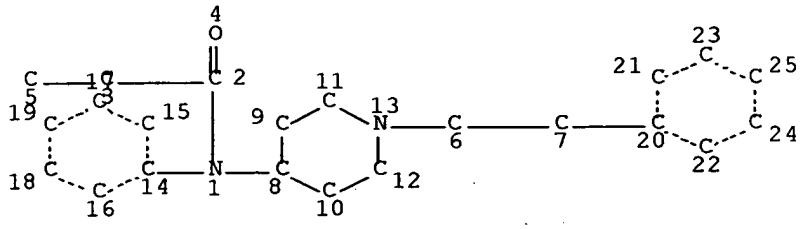

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L18            4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19           36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22           15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23           21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L26         4354 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L22
L27          490 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L23
L36         4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L26^OR L27)
L52      1536035 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEPARAT?/BI
L61           64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L36 (L) PREP/RL
L66              TRANSFER  PLU=ON  L61 1- PN :       55 TERMS
L67           12 SEA FILE=USPATFULL ABB=ON  PLU=ON  L66
L68              TRANSFER  PLU=ON  L61 1- AP :       49 TERMS
L69           13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L68
L70           13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L67 OR L69
L76            8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L52


=> d stat que L78
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L4             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  1443-54-5
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(
                 2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
L10            3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 OR L4 OR L5
L13              STR
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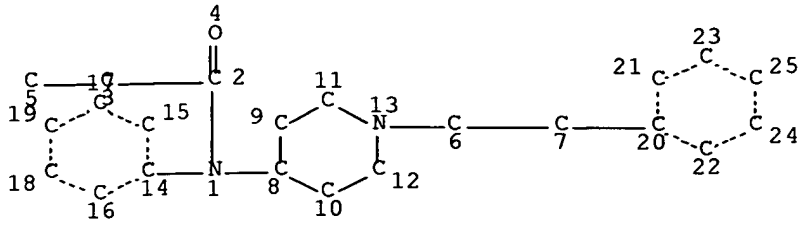

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L20	13	SEA FILE=REGISTRY ABB=ON PLU=ON L19 AND NC<2
L22	15	SEA FILE=REGISTRY ABB=ON PLU=ON L20 OR L10
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L36	4765	SEA FILE=ZCAPLUS ABB=ON PLU=ON (L26 OR L27)
L48	187446	SEA FILE=HCAPLUS ABB=ON PLU=ON ?LIQUID CHROMATOG?/BI
L51	859647	SEA FILE=HCAPLUS ABB=ON PLU=ON PURIF?/BI
L52	1536035	SEA FILE=HCAPLUS ABB=ON PLU=ON SEPARAT?/BI
L55	195334	SEA FILE=HCAPLUS ABB=ON PLU=ON HPLC/BI
L61	64	SEA FILE=HCAPLUS ABB=ON PLU=ON L36 (L) PREP/RL
L66		TRANSFER PLU=ON L61 1- PN : 55 TERMS
L67	12	SEA FILE=USPATFULL ABB=ON PLU=ON L66
L68		TRANSFER PLU=ON L61 1- AP : 49 TERMS
L69	13	SEA FILE=USPATFULL ABB=ON PLU=ON L68
L70	13	SEA FILE=USPATFULL ABB=ON PLU=ON L67 OR L69
L71	2	SEA FILE=USPATFULL ABB=ON PLU=ON L70 AND L48
L72	7	SEA FILE=USPATFULL ABB=ON PLU=ON L70 AND L55
L73	5	SEA FILE=USPATFULL ABB=ON PLU=ON L70 AND L31
L74	7	SEA FILE=USPATFULL ABB=ON PLU=ON (L71 OR L72 OR L73)
L75	8	SEA FILE=USPATFULL ABB=ON PLU=ON L70 AND L51
L76	8	SEA FILE=USPATFULL ABB=ON PLU=ON L70 AND L52
L77	9	SEA FILE=USPATFULL ABB=ON PLU=ON (L74 OR L75 OR L76)
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=> d stat que L80

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L5	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PROPANAMIDE, N-PHENYL-N-(1-(2-PHENYLETHYL)-4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN
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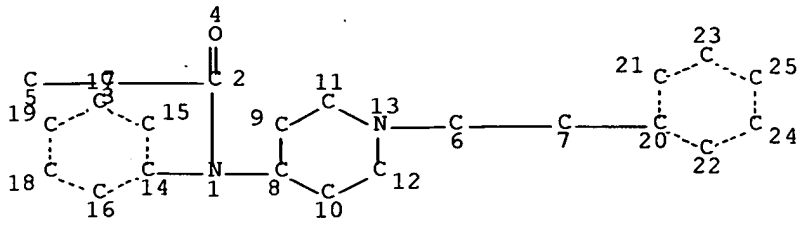

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L18            4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 AND C>22
L19           36 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20           13 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 AND NC<2
L22           15 SEA FILE=REGISTRY ABB=ON  PLU=ON  L20 OR L10
L23           21 SEA FILE=REGISTRY ABB=ON  PLU=ON  L19 NOT L22
L26         4354 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L22
L27          490 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  L23
L31        70356 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  REVERS?/BI (W) PHASE#/BI
L36         4765 SEA FILE=ZCAPLUS ABB=ON  PLU=ON  (L26 OR L27)
L48       187446 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L51       859647 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PURIF?/BI
L52      1536035 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SEPARAT?/BI
L55       195334 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HPLC/BI
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L68              TRANSFER  PLU=ON  L61 1- AP :      49 TERMS
L69           13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L68
L70           13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L67 OR L69
L71            2 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L48
L72            7 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L55
L73            5 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L31
L74            7 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L71 OR L72 OR L73)
L75            8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L51
L76            8 SEA FILE=USPATFULL ABB=ON  PLU=ON  L70 AND L52
L77            9 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L74 OR L75 OR L76)
L79         4705 SEA FILE=USPATFULL ABB=ON  PLU=ON  FENTANYL
L80            9 SEA FILE=USPATFULL ABB=ON  PLU=ON  L77 AND L79


=> s (L71 or L72 or L73 or L75 or L76 or L78 or L80) not L107
L111           8 (L71 OR L72 OR L73 OR L75 OR L76 OR L78 OR L80) NOT L107

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Dec 21, 2007 (20071221/UP).

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FILE 'ZCAPLUS' ENTERED AT 12:11:51 ON 28 DEC 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'HCAPLUS' ENTERED AT 12:11:51 ON 28 DEC 2007
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FILE 'USPATFULL' ENTERED AT 12:11:51 ON 28 DEC 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L109
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PROCESSING COMPLETED FOR L111
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ANSWERS '17-48' FROM FILE HCAPLUS
ANSWERS '49-56' FROM FILE USPATFULL

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L112 ANSWER 1 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:57702 ZCAPLUS Full-text
DOCUMENT NUMBER: 138:264887
TITLE: Characterization of chromatographic supports for the analysis of basic compounds
AUTHOR(S): Stella, Cinzia; Seuret, Patrick; Rudaz, Serge; Carrupt, Pierre-Alain; Gauvrit, Jean-Yves; Lanteri, Pierre; Veuthey, Jean-Luc
CORPORATE SOURCE: Laboratory of Pharmaceutical Analytical Chemistry-University of Geneva, Geneva, 1211/4, Switz.
SOURCE: Journal of Separation Science (2002), 25(18), 1351-1363
CODEN: JSSCCJ; ISSN: 1615-9306
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reversed-phase liquid chromatog. (RP-HPLC) has become a powerful and widely employed technique for the anal. of a great variety of substances and, in particular, of basic compds. These compds. are present in various areas. In pharmacy, 80% of drugs possess a basic function. Basic compds. can strongly interact with free silanol groups on the surface of the silica particles. These ion exchange interactions produce peak tailing which affects resolution, sensitivity, and reproducibility. For these reasons, many new stationary phases were designed to reduce access to silanol groups. The main problem facing the analyst is to effectively select the best column for a particular type of separation To characterize and evaluate the properties of these packings, several tests are proposed in the literature, which can be divided into two main categories: general tests and particular tests. A particular test was developed for the characterization of base deactivated RP-HPLC stationary phases. For this purpose, a set of 14 basic test substances was selected and five different chromatog. supports were tested with three isocratic mobile phases. Also, to undertake a complete characterization of these supports, batch and column reproducibility were also studied. Principal

Component Anal. was applied to evaluate both the performance of the test compds. and of the stationary phases.

CC 80-4 (Organic Analytical Chemistry)
Section cross-reference(s): 64

IT Principal component analysis
Reversed phase HPLC stationary phases
(characterization of chromatog. supports for the anal. of basic compds.)

IT 52-26-6, Morphine hydrochloride 54-11-5, Nicotine 76-57-3, Codeine 100-46-9, Benzylamine, analysis 110-86-1, Pyridine, analysis 130-89-2, Quinine hydrochloride 147-24-0, Diphenhydramine hydrochloride 300-62-9, Amphetamine 614-39-1, Procainamide hydrochloride 894-71-3, Nortriptyline hydrochloride ***990-73-8***, Fentanyl citrate 1095-90-5, Methadone hydrochloride 1722-62-9, Mepivacaine hydrochloride 3858-89-7, Chloroprocaine hydrochloride
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(analyte; characterization of chromatog. supports for the anal. of basic compds.)

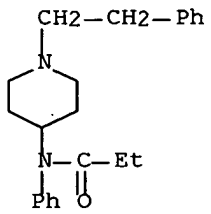
IT ***990-73-8***, Fentanyl citrate
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(analyte; characterization of chromatog. supports for the anal. of basic compds.)

RN 990-73-8 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (CA INDEX NAME)

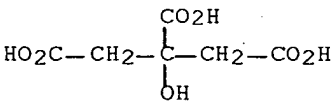
CM 1

CRN 437-38-7
CMF C22 H28 N2 O



CM 2

CRN 77-92-9
CMF C6 H8 O7



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 2 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 1999:404388 ZCAPLUS Full-text
DOCUMENT NUMBER: 131:149399
TITLE: Development and validation of an HPLC assay for fentanyl and related substances in fentanyl citrate injection, USP
AUTHOR(S): Lambropoulos, John; Spanos, George A.; Lazaridis, Nick V.; Ingallinera, Thomas S.; Rodriguez, Vonda K.
CORPORATE SOURCE: Analytical Method Development and Validation, AAI, Inc., Wilmington, NC, 28405, USA
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (1999), 20(4), 705-716
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The stability indicating properties of the USP method for the determination of fentanyl in fentanyl citrate injections were evaluated by analyzing the fentanyl drug substance and product after acid, hydrogen peroxide, heat, and light treatment. N-phenyl-N-(4-piperidinyl)propionamide (PPA), which is a known degradation product/process impurity of fentanyl, was not adequately resolved from the fentanyl peak, and mobile phase adjustments did not improve the resolution Therefore, the USP method did not meet the requirements for a stability-indicating assay. In addition, the wavelength in the USP method was too high (230 nm) to provide adequate levels for the quantitation of the related substances of fentanyl and, in addition, the acetate ions in the mobile phase could interfere with a lower wavelength detection. Therefore, an isocratic, reversed-phase stability-indicating HPLC method for the determination of fentanyl and related substances in fentanyl citrate injection, USP was developed and validated. The chromatog. conditions used were an Inertsil C8 5-μ column (25 cm + 4.6 mm), a mobile phase of 0.23% aqueous HClO4-MeCN (65:35) with UV detection at 206 nm. Under the chromatog. conditions of the method, PPA and 7 other known process impurities were separated from the drug. Degradation studies showed that the active compound eluted as a spectrally pure peak resolved from its degradation products.

CC 64-3 (Pharmaceutical Analysis)
Section cross-reference(s): 63

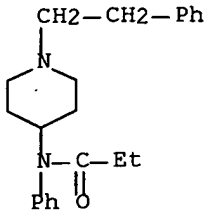
IT Decomposition
Photolysis
Reversed phase HPLC
(HPLC determination of fentanyl and related substances in fentanyl citrate injection)

IT 103-63-9, 2-Bromoethylbenzene ***437-38-7***, Fentanyl 1155-56-2, 4-Anilino-1-benzylpiperidine 1474-02-8 1609-66-1, N-Phenyl-N-(4-piperidinyl)propionamide 1796-40-3 3258-84-2 21409-26-7 23056-29-3, 4-Anilinopiperidine
RL: ANT (Analyte); ANST (Analytical study)
(HPLC determination of fentanyl and related substances in fentanyl citrate injection)

IT ***990-73-8***, Fentanyl citrate
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HPLC determination of fentanyl and related substances in fentanyl citrate injection)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(HPLC determination of fentanyl and related substances in fentanyl citrate injection)

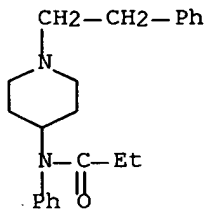
RN 437-38-7 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



IT ***990-73-8,*** Fentanyl citrate
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HPLC determination of fentanyl and related substances in fentanyl citrate injection)
RN 990-73-8 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (CA INDEX NAME)

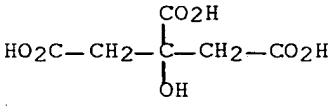
CM 1

CRN 437-38-7
CMF C22 H28 N2 O



CM 2

CRN 77-92-9
CMF C6 H8 O7



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 3 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 1997:101923 ZCAPLUS Full-text
DOCUMENT NUMBER: 126:196162
TITLE: Uniform solid-phase extraction procedure for toxicological drug screening in serum and urine by HPLC with photodiode-array detection
AUTHOR(S): Lai, Chi-Kong; Lee, Ting; Au, Kam-ming; Chan, Albert Yan-Wo
CORPORATE SOURCE: Dep. Pathology, Princess Margaret Hospital, Lai Chi Kok, Hong Kong
SOURCE: Clinical Chemistry (Washington, D. C.) (1997), 43(2), 312-325
CODEN: CLCHAU; ISSN: 0009-9147
PUBLISHER: American Association for Clinical Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this HPLC-diode-array detection method for toxicol. drug screening, a mixed-mode solid-phase extraction procedure is optimized for isolation of a broad range of drugs from serum and urine. Basic, neutral, and weakly acidic drugs are uniformly recovered. The extract from the solid-phase cartridge is readily injected to a reversed-phase HPLC column for separation by gradient elution. Unknown drugs and metabolites in urine and serum samples from acute drug poisoning cases are rapidly identified by matching their retention times and UV spectra with hundreds of reference compds. in the library. Urine metabolites of common toxicants from various medications and drugs of abuse are recorded, with their changes of retention times and UV spectra as related to their metabolic transformations. Glucuronide conjugates of common benzodiazepines, tricyclic antidepressants, and beta-blockers are examined directly without chemical or enzymic hydrolysis. The system is reliable for diverse clin. investigations of drug overdoses, drug-induced psychoses, and substance abuse.

CC 4-2 (Toxicology)
Section cross-reference(s): 1

IT Blood analysis
Drug metabolism
Drugs of abuse
Forensic chemistry
Poisoning, biological
Reversed phase HPLC
UV and visible spectroscopy
Urine analysis
(solid-phase extraction procedure for toxicol. drug screening in serum and urine by HPLC with photodiode-array detection)

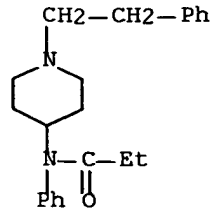
IT 50-06-6, Phenobarbital, biological studies 50-36-2, Cocaine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 51-06-9, Procainamide 51-55-8, Atropine, biological studies 52-01-7, Spironolactone 52-53-9, Verapamil 52-86-8, Haloperidol 53-86-1, Indomethacin 56-54-2, Quinidine 56-75-7, Chloramphenicol 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-42-1, Pethidine 57-43-2, Amobarbital 57-44-3, Barbital 58-08-2, Caffeine, biological studies 58-25-3, Chlordiazepoxide 58-39-9, Perphenazine 58-55-9, Theophylline, biological studies 58-73-1, Diphenhydramine 59-42-7, Phenylephrine 60-87-7, Promethazine 61-68-7, Mefenamic acid 64-77-7, Tolbutamide 69-72-7, biological studies 72-44-6, Methaqualone 72-69-5, Nortriptyline 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-73-3, Secobarbital 76-99-3, Methadone 77-02-1, Aprobarbital 77-09-8, Phenolphthalein 77-10-1, Phencyclidine 84-96-8, Trimeprazine 86-21-5, Pheniramine 86-22-6, Brompheniramine

86-54-4, Hydralazine 90-82-4, Pseudoephedrine 92-12-6, Phenyltoloxamine 93-14-1, Guaifenesin 94-78-0, Phenazopyridine 103-90-2, Acetaminophen 113-45-1, Methylphenidate 113-53-1, Dothiepin 122-09-8, Phentermine 125-33-7, Primidone 125-40-6, Butabarbital 125-71-3, Dextromethorphan 132-22-9 137-58-6, Lidocaine 144-11-6, Benzhexol 146-54-3, Triflupromazine 298-46-4, Carbamazepine 299-42-3, Ephedrine 300-62-9, Amphetamine 359-83-1, Pentazocine 364-62-5, Metoclopramide ***437-38-7***, Fentanyl 438-60-8, Protriptyline 439-14-5, Diazepam 458-24-2, Fenfluramine 465-65-6, Naloxone 469-62-5, Propoxyphene 479-92-5, Propyphenazone 509-67-1, Pholcodine 519-09-5, Benzoylecgonine 525-66-6, Propranolol 537-46-2, Methamphetamine 552-79-4, Methylephedrine 604-75-1, Oxazepam 723-46-6, Sulfamethoxazole 738-70-5, Trimethoprim 739-71-9, Trimipramine 846-49-1, Lorazepam 846-50-4, Temazepam 848-75-9, Lormetazepam 1622-61-3, Clonazepam 1668-19-5, Doxepin 1977-10-2, Loxapine 2062-78-4, Pimozide 2622-26-6, Pericyazine 2709-56-0, Flupenthixol 2955-38-6, Prazepam 3703-76-2, Cloperastine 3737-09-5, Disopyramide 4205-90-7, Clonidine 5588-33-0, Mesoridazine 5786-21-0, Clozapine 6740-88-1, Ketamine 7416-34-4, Molindone 10262-69-8, Maprotiline 12794-10-4D, Benzodiazepine, derivs. 14028-44-5, Amoxapine 14838-15-4, Phenylpropanolamine 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 17617-23-1, Flurazepam 19794-93-5, Trazodone 21829-25-4, Nifedipine 22204-53-1, Naproxen 22316-47-8, Clobazam 24166-13-0, Cloxazolam 24219-97-4, Mianserin 28981-97-7, Alprazolam 28981-97-7D, Alprazolam, hydroxy compds. 29122-68-7, Atenolol 32795-44-1, N-Acetylprocainamide 36505-84-7, Buspirone 37517-30-9, Acebutolol 41708-72-9, Tocainide 42200-33-9, Nadolol 42399-41-7, Diltiazem 42542-10-9, MDMA 43200-80-2, Zopiclone 50679-08-8, Terfenadine 51384-51-1, Metoprolol 51481-61-9, Cimetidine 52463-83-9, Pinazepam 52485-79-7, Buprenorphine 53772-83-1, Zuclopenthixol 54143-55-4, Flecainide 54739-18-3, Fluvoxamine 57574-09-1, Amineptine 59467-70-8, Midazolam 59729-33-8, Citalopram 61869-08-7, Paroxetine 65110-93-2, Dihydroxycodeine 65277-42-1, Ketoconazole 66357-35-5, Ranitidine 71320-77-9, Moclobemide 78755-81-4, Flumazenil 79617-96-2, Sertraline 82419-36-1, Ofloxacin 83891-03-6, Norfluoxetine 106266-06-2, Risperidone
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); ANST (Analytical study); BIOL (Biological study)
(solid-phase extraction procedure for toxicol. drug screening in serum and urine by HPLC with photodiode-array detection)

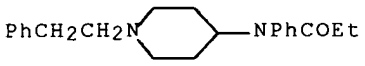
IT ***437-38-7***, Fentanyl
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); ANST (Analytical study); BIOL (Biological study)
(solid-phase extraction procedure for toxicol. drug screening in serum and urine by HPLC with photodiode-array detection)

RN 437-38-7 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



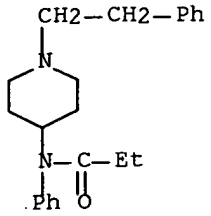
L112 ANSWER 4 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 1984:428365 ZCAPLUS Full-text
DOCUMENT NUMBER: 101:28365
ORIGINAL REFERENCE NO.: 101:4417a,4420a
TITLE: Reversed-phase high-performance ***liquid chromatographic*** separation of fentanyl homologs and analogs. I. An optimized isocratic chromatographic system utilizing absorbance ratioing
AUTHOR(S): Lurie, Ira S.; Allen, Andrew C.; Issaq, Haleem J.
CORPORATE SOURCE: Spec. Test. Res. Lab., Drug Enforcement Adm., McLean, VA, 22102, USA
SOURCE: Journal of Liquid Chromatography (1984), 7(3), 463-73
CODEN: JLCHD8; ISSN: 0148-3919
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB An optimized isocratic chromatog. system was developed using overlapping resolution mapping for the reversed-phase ***separation*** of 25 analogs and homologs of fentanyl (I) [***437-38-7***]. The system consisted of a Partisil 10-ODS-3 column with a quaternary mobile phase consisting of phosphate buffer, MeOH, MeCN and THF. All 26 compds. were distinguished when UV detection at 215 nm was employed in series with UV detection at 230 nm.

CC 64-3 (Pharmaceutical Analysis)
ST fentanyl analog detn ***liq chromatog***; UV detection chromatog fentanyl
IT Pharmaceutical analysis
(of fentanyl analogs and homologs, by high-performance ***liquid chromatog.***, absorbance ratioing in)
IT ***437-38-7*** 1237-52-1 1474-02-8 1640-10-4 1838-67-1 2141-47-1 3258-84-2 42045-77-2 47480-47-7 59708-54-2 79146-56-8 79704-88-4 90736-10-0 90736-11-1 90736-12-2 90736-13-3 90736-14-4 90736-15-5 90736-16-6 90736-17-7 90736-18-8 90736-19-9 90736-20-2 90736-21-3 90736-22-4 90736-23-5
RL: PROC (Process)
(***separation*** of, by high-performance ***liquid chromatog.***, absorbance ratioing in)
IT ***437-38-7***
RL: PROC (Process)
(***separation*** of, by high-performance ***liquid chromatog.***, absorbance ratioing in)
RN 437-38-7 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 5 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1984:603780 ZCAPLUS Full-text
DOCUMENT NUMBER: 101:203780
ORIGINAL REFERENCE NO.: 101:30703a,30706a
TITLE: Radioreceptor assay of narcotic analgesics in serum
AUTHOR(S): Grevel, Joachim; Thomas, Jeff; Richards, Mark L.; Sadee, Wolfgang
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143, USA
SOURCE: Pharmaceutical Research (1984), (5), 209-14
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive radioreceptor assay (RRA) to determine the serum concns. of fentanyl citrate [***990-73-8***], pentazocine [359-83-1], and morphine [57-27-2] was developed on the basis of the drugs' competition with a labeled tracer (3H-naloxone) for the membrane-bound opioid receptor in rat brain homogenates. The binding data were computer-fitted to a standard curve by means of nonlinear least square regression. Sensitivity of the assay, applied directly to serum samples without extraction, was limited to approx. 3, 5 and 25 ng/mL for fentanyl, morphine and pentazocine, resp., because of endogenous plasma constituents that interfere with the opioid receptor binding. With the use of petroleum ether extraction the sensitivity was improved to 0.3 ng/mL fentanyl and 3 ng/mL pentazocine (0.3-mL serum samples). No RRA-active metabolites were detectable after ***HPLC separation*** of serum from a patient treated with fentanyl. The plasma concentration-time course of fentanyl in a patient, measured by RRA, was similar to that obtained by a radioimmunoassay. The RRA represents a general procedure for the detection of clin. used opioid analgesics and their active metabolites.
CC 1-1 (Pharmacology)

L112 ANSWER 6 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:401450 ZCAPLUS Full-text
DOCUMENT NUMBER: 147:86179
TITLE: Pharmacokinetics of propofol in children with ventricular septal defect
AUTHOR(S): Gu, Hong-bin; Chen, Yu; Wang, Xiang-rui
CORPORATE SOURCE: Department of Anesthesiology, Shanghai Children's Medical Center, Shanghai Jiaotong University School of Medicine, Shanghai, 200127, Peop. Rep. China
SOURCE: Zhonghua Mazuixue Zazhi (2007), 27(1), 51-53
CODEN: ZMZADD; ISSN: 0254-1416
PUBLISHER: Hebeisheng Yixue Kexueyuan Qingbaosuo
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The pharmacokinetics of propofol in children with ventricular septal defect (VSD) was studied during cardiopulmonary bypass (CPB). Forty ASA I or II

children with VSD, aged 1-6 y weighing 10-22 kg, were undergone VSD repair under CPB and included in this study. The patients were premedicated with oral administration of 0.5 mg/kg midazolam. Anesthesia was induced by 20 μg/kg fentanyl, 0.1 mg/kg midazolam, and 0.1 mg/kg vecuronium bromide, and maintained by isoflurane-N2O-O2 (1: 49: 50) and intermittent i.v. injection of fentanyl after tracheal intubation. Propofol (3 mg/kg) was injected i.v. within 30 s before CPB. The venous blood samples were taken at 0, 1, 2, 4, 6, 10, 15, 30, 60, 90, 150, 210, 300, 420 min after i.v. injection of propofol. The concns. of propofol in plasma were determined by RP-HPLC with fluorescence detector. The data were analyzed with 3P87 software. The pharmacokinetics of propofol in children with VSD undergoing CPB was best described by a two-compartment model and first-order elimination rate. The determined values of CL, Vc, Vd, t1/2α, and t1/2β were (0.070 ± 0.021) L/(kg • min), (1.24 ± 0.25) L/kg, (38 ± 6) L/kg, (4.5 ± 0.8) min, and (148 ± 26) min, resp. There was no linear regression relationship between pharmacokinetic parameters and demog. data (age, body weight, BSA) except height. The pharmacokinetics of prepofol in children with VSD undergoing CPB is different from that in adult, for the t1/2α and t1/2β are prolonged, the Vd is larger, and the CL is slower in children than in adults.

CC 1-2 (Pharmacology)

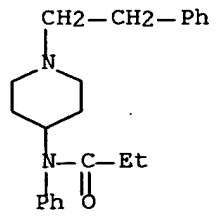
IT Cardiopulmonary bypass
Human
Pharmacokinetics
Reversed phase HPLC
(pharmacokinetics of propofol in children with ventricular septal defect)

IT ***437-38-7***, Fentanyl 2078-54-8, Propofol 50700-72-6, Vecuronium bromide 59467-70-8, Midazolam
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of propofol in children with ventricular septal defect)

IT ***437-38-7***, Fentanyl
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of propofol in children with ventricular septal defect)

RN 437-38-7 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 7 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1237748 ZCAPLUS Full-text
DOCUMENT NUMBER: 147:45039
TITLE: Determination of propofol in human serum by improved reversed phase high-performance liquid chromatography

with fluorescence detection

AUTHOR(S): Fan, Ying-ying; Xu, Li-xian; Wen, Ai-dong; Zhang, Hui; Liu, Chun-ran; Li, Wei; Mei, Xiao-peng

CORPORATE SOURCE: Dep. Anesthesiol., Stomatol. Hosp., Fourth Military Med. Univ., Xi'an, 710033, Peop. Rep. China

SOURCE: Nanfang Yike Daxue Xuebao (2006), 26(10), 1510-1512
CODEN: NYDXAN; ISSN: 1673-4254

PUBLISHER: Nanfang Yike Daxue Xuebao Bianjibu

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The objective of this paper was to develop a new high-performance liquid chromatog. (HLPC) method for determination of propofol in human serum. Human serum samples were precipitated with 20% perchloric acid and centrifuged to obtain 50 μl of the supernatant for anal. by HPLC coupled with fluorescence detection. The anal. was performed with C18 reversed-phase column using a acetonitrile-water (90 : 10) phase delivered at 1.0 mL/min, with the excitation wavelength of 276 nm and emission wavelength of 310 nm. Results showed that the calibration curves were linear (r = 0.9975) within the concentration range of 0.05-10 μg/mL. The limit of propofol quantification was 50 ng/mL, and the intra- and inter-day precisions were between 4.78 and 6.59. In conclusion, this method was accurate, sensitive and simple for propofol determination in clin. anesthesia.

CC 1-1 (Pharmacology)

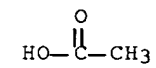
IT Blood serum
Fluorometry
Human
Reversed phase HPLC
(determination of propofol in human serum by improved reversed phase high-performance liquid chromatog. with fluorescence detection)

IT ***64-19-7***, Acetic acid, analysis ***75-05-8***, Acetonitrile, analysis 89-83-8, Thymol 7601-90-3, Perchloric acid, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(determination of propofol in human serum by improved reversed phase high-performance liquid chromatog. with fluorescence detection)

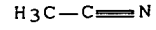
IT 51-55-8, Atropine, occurrence ***437-38-7***, Fentanyl 50700-72-6, Vecuronium bromide 59467-70-8, Midazolam
RL: OCU (Occurrence, unclassified); OCCU (Occurrence)
(determination of propofol in human serum by improved reversed phase high-performance liquid chromatog. with fluorescence detection)

IT ***64-19-7***, Acetic acid, analysis ***75-05-8***, Acetonitrile, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(determination of propofol in human serum by improved reversed phase high-performance liquid chromatog. with fluorescence detection)

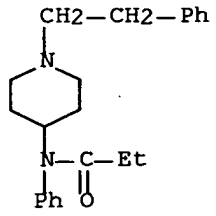
RN 64-19-7 ZCAPLUS
CN Acetic acid (CA INDEX NAME)



RN 75-05-8 ZCAPLUS
CN Acetonitrile (CA INDEX NAME)



IT ***437-38-7,*** Fentanyl
RL: OCU (Occurrence, unclassified); OCCU (Occurrence)
(determination of propofol in human serum by improved reversed phase high-performance liquid chromatog. with fluorescence detection)
RN 437-38-7 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 8 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:255294 ZCAPLUS Full-text
DOCUMENT NUMBER: 141:128989
TITLE: Analysis of basic compounds at high pH values by reversed-phase liquid chromatography
AUTHOR(S): Stella, Cinzia; Rudaz, Serge; Mottaz, Manuel; Carrupt, Pierre-Alain; Veuthey, Jean-Luc
CORPORATE SOURCE: Laboratory of Pharmaceutical Analytical Chemistry - School of Pharmacy, University of Geneva, Geneva, 1211/4, Switz.
SOURCE: Journal of Separation Science (2004), 27(4), 284-292
CODEN: JSSCCJ; ISSN: 1615-9306
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Reversed phase high performance liquid chromatog. (RPLC) is currently the method of choice for the anal. of basic compds. However, with traditional silica materials, secondary interactions between the analyte and residual silanols produce peak tailing which can neg. affect resolution, sensitivity, and reproducibility. In order to reduce these secondary interactions, which comprise ion exchange, hydrogen bonding, and London forces interactions, chromatog. analyses can be carried out at low or high pH values where silanol groups and basic compds. are mostly uncharged. The chromatog. behavior of a particular bidentate stationary phase, Zorbax Extend C18, was studied with a set of basic and neutral compds. Thanks to a higher chemical stability than traditional silica based supports, analyses were carried out with a high pH mobile phase, which represents a good alternative to the acidic mobile phases generally used to reduce ion exchange interactions. The performance of this bidentate stationary phase was also compared with that of other supports and it was proved that it is advantageous to work with high pH mobile phases when analyzing basic compds.

CC 64-3 (Pharmaceutical Analysis)
IT Pharmaceutical analysis

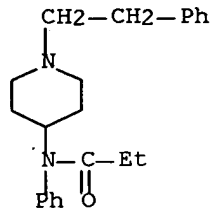
Reversed phase HPLC
(anal. of basic compds. at high pH values by reversed-phase liquid chromatog.)

IT 51-06-9, Procainamide 51-64-9 54-11-5, Nicotine 57-27-2, Morphine, analysis 58-73-1, Diphenhydramine 72-69-5 76-57-3, Codeine 76-99-3, Methadone 96-88-8, Mepivacaine 100-46-9, Benzylamine, analysis 110-86-1, Pyridine, analysis 130-95-0, Quinine 133-16-4, Chloroprocaine 299-42-3, Ephedrine ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(anal. of basic compds. at high pH values by reversed-phase liquid chromatog.)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(anal. of basic compds. at high pH values by reversed-phase liquid chromatog.)

RN 437-38-7 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 9 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:693231 ZCAPLUS Full-text
DOCUMENT NUMBER: 137:222198
TITLE: Elogdoct:a tool for lipophilicity determination in drug discovery basic and neutral compounds
INVENTOR(S): Lombardo, Franco; Shalaeva, Marina Y.; Tupper, Karl A.
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1239280	A2	20020911	EP 2002-250906	20020211
EP 1239280	A3	20040331		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2002267647	A	20020918	JP 2002-42530	20020220
JP 3444872	B2	20030908		
US 2002161528	A1	20021031	US 2002-81784	20020221
CA 2372754	A1	20020826	CA 2002-2372754	20020222
PRIORITY APPLN. INFO.:			US 2001-271598P P	20010226

AB A RP-HPLC method for the determination of ElogDoct values for chemical compds. from retention time of each sample of the compound using log Doct =log Poct + log [1/1(1+10 pKa -pH)]. This method has been shown to be effective on a set of 90 mols.

IC ICM G01N030-02

CC 64-3 (Pharmaceutical Analysis)

IT Computer program
Lipophilicity
Reversed phase HPLC
(lipophilicity determination in drug discovery basic and neutral compds.)

IT 50-02-2, Dexamethasone 50-03-3, Hydrocortisone acetate 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-28-2, Estradiol, analysis 50-36-2, Cocaine 50-47-5, Desipramine 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, analysis 51-06-9, Procainamide 51-55-8, Atropine, analysis 52-86-8, Haloperidol 53-03-2, Prednisone 54-11-5, Nicotine 56-53-1, Diethylstilbestrol 56-54-2, Quinidine 56-75-7, Chloramphenicol 58-08-2, Caffein, analysis 58-22-0, Testosterone 58-73-1, Diphenhydramine 59-87-0, Nitrofurazone 60-80-0, Antipyrine 60-99-1, Methotrimeprazine 64-31-3, Morphine sulfate 76-57-3, Codeine 77-36-1, Chlorthalidone 91-20-3, Naphthalene, analysis 91-22-5, Quinoline, analysis 94-24-6, Tetracaine 98-86-2, Acetophenone, analysis 103-90-2, Acetaminophen 108-43-0, 3-Chlorophenol 126-07-8, Griseofulvin 132-22-9, Chlorpheniramine 133-67-5, Trichlormethiazide 137-58-6, Lidocaine 146-54-3, Triflupromazine 298-46-4, Carbamazepine 315-30-0, Allopurinol 342-69-8, Methylthioinosine 364-62-5, Metoclopramide 396-01-0, Triamterene 439-14-5, Diazepam 443-48-1, Metronidazole 525-66-6, Propranolol 591-35-5, 3,5-Dichlorophenol 738-70-5, Trimethoprim 846-49-1, Lorazepam 848-75-9, Lormetazepam ***990-73-8***, Fentanyl citrate 1951-25-3, Amiodarone 2259-96-3, Cyclothiazide 2323-36-6, Deprenyl 2398-96-1, Tolnaftate 3737-09-5, Disopyramide 3930-20-9, Sotalol 4205-90-7, Clonidine 5332-24-1, 3-Bromoquinoline 5786-21-0, Clozapine 6236-05-1, Nifuroxime 6493-05-6, Pentoxifylline 13655-52-2, Alprenolol 15318-45-3, Thiamphenicol 19794-93-5, Trazodone 21829-25-4, Nifedipine 23031-32-5, Terbutaline sulfate 23593-75-1, Clotrimazole 28797-61-7, Pirenzepine 28981-97-7, Alprazolam 31828-71-4, Mexiletine 37517-30-9, Acebutolol 42399-41-7, Diltiazem 51012-32-9, Tiapride 51384-51-1, Metoprolol 51481-61-9, Cimetidine 54063-53-5, Propafenone 54143-55-4, Flecainide 60628-96-8, Bifonazole 66357-35-5, Ranitidine 69014-14-8, Tiotidine 73590-58-6, Omeprazole 76963-41-2, Nizatidine 86386-73-4, Fluconazole 88150-42-9, Amlodipine 103628-46-2, Sumatriptan 106266-06-2, Risperidone
RL: ANT (Analyte); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(lipophilicity determination in drug discovery basic and neutral compds.)

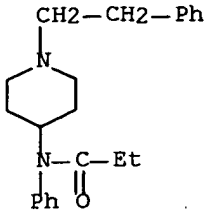
IT ***990-73-8***, Fentanyl citrate
RL: ANT (Analyte); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(lipophilicity determination in drug discovery basic and neutral compds.)

RN 990-73-8 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (CA INDEX NAME)

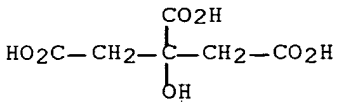
CM 1

CRN 437-38-7
CMF C22 H28 N2 O



CM 2

CRN 77-92-9
CMF C6 H8 O7



L112 ANSWER 10 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:457579 ZCAPLUS Full-text
DOCUMENT NUMBER: 135:200312
TITLE: ElogDoct: A Tool for Lipophilicity Determination in Drug Discovery. 2. Basic and Neutral Compounds
AUTHOR(S): Lombardo, Franco; Shalaeva, Marina Y.; Tupper, Karl A.; Gao, Feng
CORPORATE SOURCE: Groton Laboratories, Molecular Properties Group and Mathematical and Statistical Sciences Group, Pfizer Global Research and Development, Groton, CT, 06340, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(15), 2490-2497
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We present an RP-HPLC method for the determination of the octanol-water distribution coeffs. at pH 7.4, as log Doct7.4 values, for neutral and basic drugs, which combines ease of operation with high accuracy. The method is shown to work for a training set of 90 mols. comprised largely of drugs, and it was also applied to a test set of 10 proprietary compds. This work expands the applicability of the method presented in our earlier report, for the determination of logPoct for neutral compds. (J. Med. Chemical 2000, 43, 2922-2928), and it offers the same general features but widens the scope. Generally, the method (i) is compound sparing (≤1 mL of a 50-100 μg/mL solution needed), (ii) is insensitive to concentration and phase ratio effects observed in some shake-flask detns., (iii) is amenable to rapid detns. (≤20 min on average), (iv) is insensitive to impurities, (v) possesses a wide lipophilicity range (>7 log Doct7.4 units), and (vi) offers a good accuracy, (vii) an excellent reproducibility, (viii) and an excellent potential for automation. To the best of our knowledge, a similar performance, on a set of

noncongeneric drugs, has not been previously reported. We refer to the value generated via this method as ElogDoct.

CC 63-5 (Pharmaceuticals)

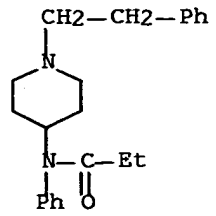
IT Lipophilicity
Reversed phase HPLC
(ElogDoct: a tool for lipophilicity determination in drug discovery)

IT 50-02-2, Dexamethasone 50-03-3, Hydrocortisone-21 acetate 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-28-2, Estradiol, properties 50-36-2, Cocaine 50-47-5, Desipramine 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, properties 51-06-9, Procainamide 51-55-8, Atropine, properties 52-86-8, Haloperidol 53-03-2, Prednisone 54-11-5, Nicotine 56-53-1, Diethylstilbestrol 56-54-2, Quinidine 56-75-7, Chloramphenicol 58-08-2, Caffeine, properties 58-22-0, Testosterone 58-73-1, Diphenhydramine 59-87-0, Nitrofurazone 60-80-0, Antipyrine 60-99-1, Methotrimeprazine 64-31-3, Morphine sulfate 76-57-3, Codeine 77-36-1, Chlorthalidone 91-20-3, Naphthalene, properties 91-22-5, Quinoline, properties 94-24-6, Tetracaine 98-86-2, Acetophenone, properties 103-90-2, Acetaminophen 108-43-0, 3-Chlorophenol 113-92-8, Chlorpheniramine 126-07-8, Griseofulvin 133-67-5, Trichlormethiazide 137-58-6, Lidocaine 146-54-3, Trifluprom azine 298-46-4, Carbamazepine 315-30-0, Allopurinol 342-69-8, Methylthioinosine 364-62-5, Metoclopramide 396-01-0, Triamterene ***437-38-7***, Fentanyl 439-14-5, Diazepam 443-48-1, Metronidazole 525-66-6, Propranolol 591-35-5, 3,5-Dichlorophenol 738-70-5, Trimethoprim 846-49-1, Lorazepam 848-75-9, Lormetazepam 1812-30-2, Bromazepam 1951-25-3, Amiodarone 2259-96-3, Cyclothiazide 2323-36-6, Deprenyl 2398-96-1, Tolnaftate 3737-09-5, Disopyramide 3930-20-9, Sotalol 4205-90-7, Clonidine 5332-24-1, 3-Bromo-quinoline 5786-21-0, Clozapine 6236-05-1, Nifuroxime 6493-05-6, Pentoxifylline 13655-52-2, Alprenolol 15318-45-3, Thiamphenicol 19794-93-5, Trazodone 21829-25-4, Nifedipine 23031-32-5, Terbutaline sulfate 23593-75-1, Clotrimazole 28797-61-7, Pirenzepine 28981-97-7, Alprazolam 31828-71-4, Mexiletine 37517-30-9, Acebutolol 42399-41-7, Diltiazem 51012-32-9, Tiapride 51384-51-1, Metoprolol 51481-61-9, Cimetidine 54063-53-5, Propafenone 54143-55-4, Flecainide 60628-96-8, Bifonazole 66357-35-5, Ranitidine 69014-14-8, Tiotidine 73590-58-6, Omeprazole 76963-41-2, Nizatidine 79794-75-5, Loratadine 85604-00-8, Zaltidine 86386-73-4, Fluconazole 88150-42-9, Amlodipine 103628-46-2, Sumatriptan 106266-06-2, Risperidone
RL: PRP (Properties)
(ElogDoct: a tool for lipophilicity determination in drug discovery)

IT ***437-38-7***, Fentanyl
RL: PRP (Properties)
(ElogDoct: a tool for lipophilicity determination in drug discovery)

RN 437-38-7 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)

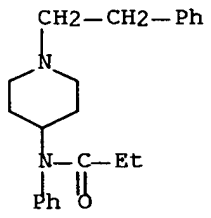


REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 11 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:553067 ZCAPLUS Full-text
DOCUMENT NUMBER: 129:272457
TITLE: Determination of fentanyl in plasma by Ion-pair RP-HPLC
AUTHOR(S): Zhang, Yanwen; Zhang, Yi; Hu, Xiaoqin
CORPORATE SOURCE: Department of Anesthesiology, Cardiovascular Institute, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, 100037, Peop. Rep. China
SOURCE: Zhongguo Yaoxue Zazhi (Beijing) (1998), 33(5), 301-303
CODEN: ZYZAEU; ISSN: 1001-2494
PUBLISHER: Zhongguo Yaoxuehui
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The determination of fentanyl concentration in plasma was studied by Ion-pair RP-HPLC on μ-Bondapak C18 column (3.9 mm x 250 mm) with H2O (containing 0.005 mol L-1 C8H17O3SNa and 0.01 mol L-1 H3PO4) : acetonitrile as mobile phase and the detection at 220 nm. Alfentanil was used as a internal standard The results showed that the mean recovery of fentanyl was 99.97%, the intra-day and inter-day RSD were all less than 8%, the linearity was ranged from 10 ng·ml-1 to 200 ng·ml-1 in plasma (r = 0.999 6) with the limit 5 ng·ml-1. This method possessed high accuracy and precision, and was sensitive and specific.

CC 9-3 (Biochemical Methods)
IT Blood analysis
Reversed phase HPLC
(determination of fentanyl in plasma by ion-pair reversed phase HPLC)
IT ***437-38-7,*** Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(determination of fentanyl in plasma by ion-pair reversed phase HPLC)
IT ***437-38-7,*** Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(determination of fentanyl in plasma by ion-pair reversed phase HPLC)
RN 437-38-7 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 12 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:803908 ZCAPLUS Full-text
DOCUMENT NUMBER: 128:107495
TITLE: Isotopic fractionation of fentanyl and its deuterated

analogs by capillary gas ***chromatography***
AUTHOR(S): Sera, Shoji; Goromaru, Tsuyoshi
CORPORATE SOURCE: Dep. Pharm. Pharm. Sci., Fukuyama Univ., Fukuyama, 792-02, Japan
SOURCE: Radioisotopes (1997), 46(12), 885-892
CODEN: RAISAB; ISSN: 0033-8303
PUBLISHER: Nippon Aisotopu Kyokai
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Isotopic fractionation of fentanyl (FT) and its deuterated analogs by gas ***chromatog.*** using capillary columns (CBP1 and CBP5) was studied. Seven kinds of analogs were labeled with 5-19 D atoms at the anilino, propionyl and/or phenylethyl group of FT. The retention times of deuterated FT in CBP1 and CBP5 columns are inversely proportional to the number of labeled D atoms in the mol. The difference in free energy changes (ΔΔG) had a linear relation with the number of labeled D atoms, except for labeling at anilino and phenylethyl group. The contribution of a D atom to the ΔΔG value is 1.13 cal/mol in CBP1 and 1.40 cal/mol in CBP5, resp. While, its contribution in the propionyl group was 2.84 cal/mol in CBP1 and 2.48 cal/mol in CBP5, resp. An important factor in separation by GC may differences in interactions between the stationary phase of the column with the 3 dimensional protrusive moiety in the mol.

CC 71-6 (Nuclear Technology)
Section cross-reference(s): 27

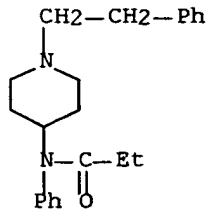
ST isotopic fractionation fentanyl deuterated analog; capillary gas ***chromatog*** isotopic fractionation

IT Capillary gas ***chromatography***
(isotopic fractionation of fentanyl and its deuterated analogs by capillary gas ***chromatog.***)

IT ***437-38-7P***, Fentanyl ***118357-29-2P 201415-22-7P 201415-23-8P 201415-24-9P 201415-25-0P 201415-26-1P 201415-27-2P***
RL: ***PUR (Purification or recovery); PREP (Preparation)***
(isotopic fractionation of fentanyl and its deuterated analogs by capillary gas ***chromatog.***)

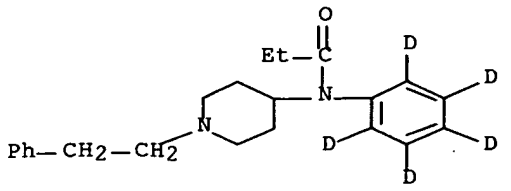
IT ***437-38-7P***, Fentanyl ***118357-29-2P 201415-22-7P 201415-23-8P 201415-24-9P 201415-25-0P 201415-26-1P 201415-27-2P***
RL: ***PUR (Purification or recovery); PREP (Preparation)***
(isotopic fractionation of fentanyl and its deuterated analogs by capillary gas ***chromatog.***)

RN 437-38-7 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)

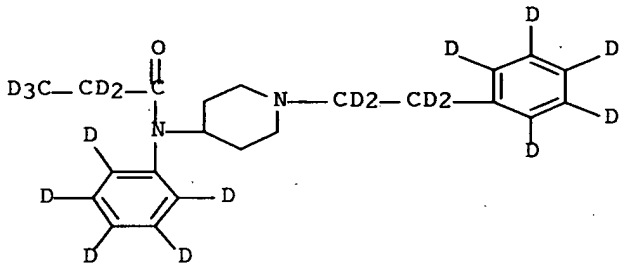


RN 118357-29-2 ZCAPLUS
CN Propanamide, N-(phenyl-d5)-N-[1-(2-phenylethyl)-4-piperidinyl]- (9CI) (CA

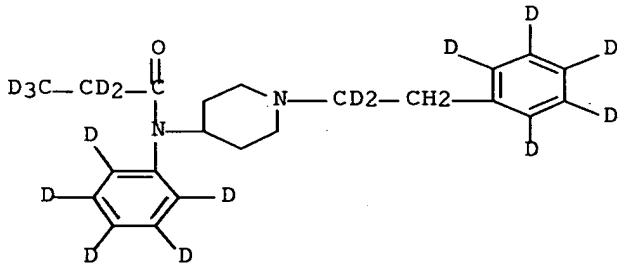
INDEX NAME)



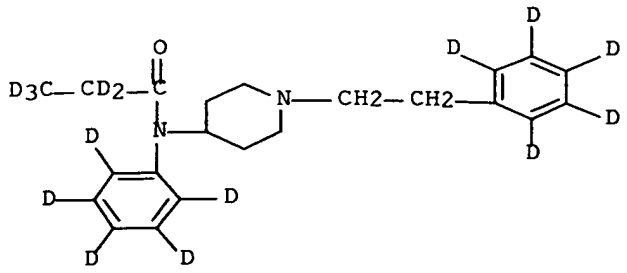
RN 201415-22-7 ZCAPLUS
CN Propanamide-2,2,3,3,3-d5, N-(phenyl-d5)-N-[1-[2-(phenyl-d5)ethyl-1,1,2,2-d4]-4-piperidinyl]- (9CI) (CA INDEX NAME)



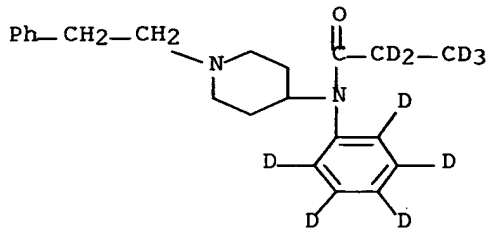
RN 201415-23-8 ZCAPLUS
CN Propanamide-2,2,3,3,3-d5, N-(phenyl-d5)-N-[1-[2-(phenyl-d5)ethyl-1,1-d2]-4-piperidinyl]- (9CI) (CA INDEX NAME)



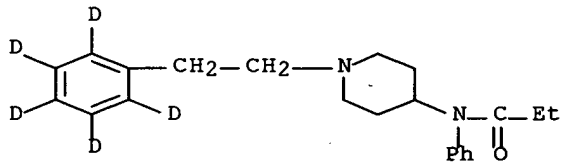
RN 201415-24-9 ZCAPLUS
CN Propanamide-2,2,3,3,3-d5, N-(phenyl-d5)-N-[1-[2-(phenyl-d5)ethyl]-4-piperidinyl]- (9CI) (CA INDEX NAME)



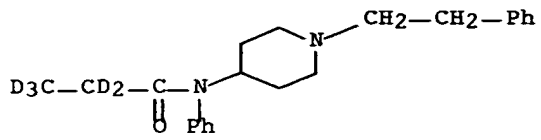
RN 201415-25-0 ZCAPLUS
CN Propanamide-2,2,3,3,3-d5, N-(phenyl-d5)-N-[1-(2-phenylethyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)



RN 201415-26-1 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-[2-(phenyl-d5)ethyl]-4-piperidinyl]- (9CI) (CA INDEX NAME)



RN 201415-27-2 ZCAPLUS
CN Propanamide-2,2,3,3,3-d5, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)



L112 ANSWER 13 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:361533 ZCAPLUS Full-text
DOCUMENT NUMBER: 125:96316
TITLE: Separation of basic drugs with non-aqueous capillary electrophoresis
AUTHOR(S): Leung, Gary N. W.; Tang, Hubert P. O.; Tso, Twinnie S. C.; Wan, Terence S. M.
CORPORATE SOURCE: Department of Chemistry, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong
SOURCE: Journal of Chromatography, A (1996), 738(1), 141-154
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

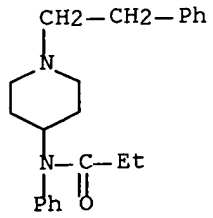
AB Capillary zone electrophoresis (CZE) was investigated in non-aqueous media. Efficient, rapid and versatile electrophoretic conditions were obtained with 20 mM ammonium acetate in acetonitrile-methanol-acetic acid (49:50:1). Using this non-aqueous medium, the baseline separation of nine morphine analogs, eleven antihistamines, eleven antipsychotics and ten stimulants could each be achieved in 6 min. The migration order observed was very different from one expected for an aqueous medium. The migration time repeatability for individual components was between 0.8 and 3.7% R.S.D. The migration time-normalized peak area had a poor precision; however, with one of the components as an internal reference, the quant. repeatability could be improved to between 2.2 and 9.1% R.S.D. The precision data appeared to be instrument dependent, as excellent results could be obtained from an instrument with better evaporation and temperature control. Alternatively, much improved speed, efficiency and precision were also achieved with tetra-n-butylammonium tetrafluoroborate as the electrolyte, albeit with reduced selectivity. The effects of the electrolyte, non-aqueous medium and applied voltage on the separation are discussed.

CC 64-3 (Pharmaceutical Analysis)

IT 50-52-2, Thioridazine 50-55-5, Reserpine 57-27-2D, Morphine, derivs. 57-42-1, Meperidine 58-40-2, Promazine 59-26-7, Nikethamide 60-87-7, Promethazine 60-99-1, Methotrimeprazine 62-67-9, Nalorphine 63-12-7, Benzquinamide 76-99-3, Methadone 77-15-6, Ethoheptazine 82-92-8, Cyclizine 82-93-9, Chlorcyclizine 82-95-1, Buclizine 86-21-5, Pheniramine 91-81-6, Tripelennamine 91-82-7, Pyrrobutamine 91-84-9 113-92-8 131-01-1, Deserpidine 152-02-3, Levallorphan 359-83-1, Pentazocine ***437-38-7***, Fentanyl 493-78-7, Methaphenilene 522-00-9, Ethopropazine 523-87-5, Dimenhydrinate 915-30-0, Diphenoxylate 3313-26-6, Thiothixene 5588-33-0, Mesoridazine 7416-34-4, Molindone
RL: ANT (Analyte); ANST (Analytical study)
(***separation*** of basic drugs by capillary electrophoresis in non-aqueous media)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(***separation*** of basic drugs by capillary electrophoresis in non-aqueous media)

RN 437-38-7 ZCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 14 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:451679 ZCAPLUS Full-text
DOCUMENT NUMBER: 122:207223
TITLE: Isolation of phentanyl from cadaver organs by acetonitrile and acetone
AUTHOR(S): Stadnichenko, E. I.; Bolotov, V. V.; Bondar, V. S.; Mamina, E. A.
CORPORATE SOURCE: Ukr. Farm. Akad., Ukraine
SOURCE: Farmatsevtichnii Zhurnal (Kiev) (1993), (4), 66-9
CODEN: FRZKAP; ISSN: 0367-3057
PUBLISHER: Zdorov'ya
DOCUMENT TYPE: Journal
LANGUAGE: Ukrainian

AB A method was worked out of isolation and quant. determination of phentanyl in cadaver organs (liver, brain) based on its extraction by acetonitrile or acetone and subsequent determination on the ***chromatograms***. The advantages of the method are shown.

CC 4-2 (Toxicology)

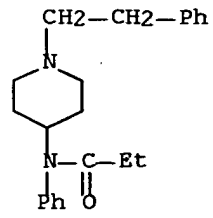
IT ***437-38-7P***, Phentanyl
RL: ANT (Analyte); ***PUR (Purification or recovery)***; ANST (Analytical study); ***PREP (Preparation)***
(phentanyl isolation from cadaver organs by acetonitrile and acetone)

IT 67-64-1, Acetone, biological studies ***75-05-8***, Acetonitrile, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(phentanyl isolation from cadaver organs by acetonitrile and acetone)

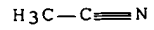
IT ***437-38-7P***, Phentanyl
RL: ANT (Analyte); ***PUR (Purification or recovery)***; ANST (Analytical study); ***PREP (Preparation)***
(phentanyl isolation from cadaver organs by acetonitrile and acetone)

RN 437-38-7 ZCAPLUS

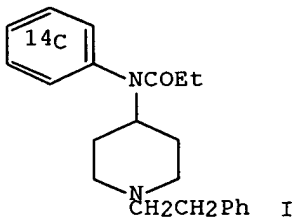
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



IT ***75-05-8***, Acetonitrile, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(phentanyl isolation from cadaver organs by acetonitrile and acetone)
RN 75-05-8 ZCAPLUS
CN Acetonitrile (CA INDEX NAME)



L112 ANSWER 15 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:233830 ZCAPLUS Full-text
DOCUMENT NUMBER: 118:233830
TITLE: Synthesis and analysis of the opioid analgesic carbon-14-labeled [14C]-fentanyl
AUTHOR(S): Bagley, Jerome R.; Wilhelm, Jeffrey A.
CORPORATE SOURCE: Anaquest Inc., Murray Hill, NJ, 07974, USA
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1992), 31(11), 945-50
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The synthesis of [14C]-fentanyl (I), the radiolabeled congener of the potent opioid analgesic chosen for utilization in drug disposition studies, is described. [14C]-Labeling was achieved in the first of two steps, a room temperature reduction of the in situ generated Schiff base from 1-phenylethyl-4-piperidone and [UL-14C]-aniline hydrochloride with sodium triacetoxyborohydride. A nearly instantaneous production of fentanyl was accomplished at room temperature with the addition of propionyl chloride. The overall radiochem. yield was 18%. The method described is efficiently adaptable for submicromolar scale while yielding a product of sufficient specific activity for in vivo studies. The solvent system use for thin layer ***chromatog.*** was superior to the USP system reported for ***chromatog.*** anal. of fentanyl. This is the first reported preparation of [14C]-fentanyl with the radiolabel in the aniline benzene ring.
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
IT ***147018-96-0P***

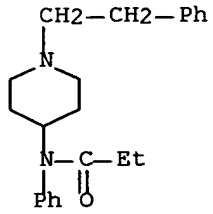
RL: SPN (Synthetic preparation); ***PREP (Preparation)***
(preparation of)

IT ***147018-96-0P***

RL: SPN (Synthetic preparation); ***PREP (Preparation)***
(preparation of)

RN 147018-96-0 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, labeled with carbon-14 (9CI) (CA INDEX NAME)



L112 ANSWER 16 OF 56 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1982:62474 ZCAPLUS Full-text

DOCUMENT NUMBER: 96:62474

ORIGINAL REFERENCE NO.: 96:10127a,10130a

TITLE: Determination of plasma fentanyl by GC-mass spectrometry and pharmacokinetic analysis

AUTHOR(S): Lin, Shen Nan; Wang, Tsent Pu F.; Caprioli, Richard M.; Mo, Benjamin P. N.

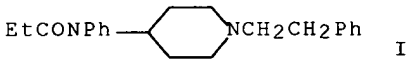
CORPORATE SOURCE: Med. Sch., Univ. Texas, Houston, TX, 77025, USA

SOURCE: Journal of Pharmaceutical Sciences (1981), 70(11), 1276-9
CODEN: JPMSAE; ISSN: 0022-3549

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB Gas ***chromatog***. (GC)-mass spectrometry was used to measure extremely low levels of fentanyl (I) [***437-38-7***] in dog plasma. fentanyl-d3 [80430-19-9] Was synthesized for use as an internal standard I was hydrolyzed to despropionylfentanyl(II) by 20% DCl in D2O. Mass spectrometric anal. of the product revealed that the mol. ion was 3 mass units higher than that of the authentic II, indicating that the deuterium exchange reactions occurred at this stage. Deuterated II was reesterified by propionyl chloride to fentanyl-d3. The drug was assayed in biol. fluids by extraction into EtOAc followed by anal. with GC-chemical-ionization mass spectrometry. The lowest measurable plasma I level is 500 pg/mL. The method is highly selective and is suitable for monitoring the time course of plasma drug levels. Evaluation of pharmacokinetic data from expts. using dogs revealed a triphasic phenomenon.

No measurable amts. of the major metabolites, II and norfentanyl, were detected.

CC 1-1 (Pharmacology)

ST fentanyl detn blood pharmacokinetics; gas ***chromatog*** mass spectrometry fentanyl

IT Blood analysis
(fentanyl determination in, by gas ***chromatog***.-mass spectrometry)

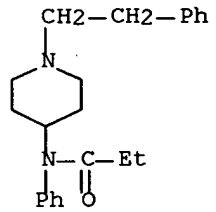
IT ***437-38-7***
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood by gas ***chromatog***.-mass spectrometry, pharmacokinetics in relation to)

IT ***80430-19-9P***
RL: SPN (Synthetic preparation); ***PREP (Preparation)***
(preparation of)

IT ***437-38-7***
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood by gas ***chromatog***.-mass spectrometry, pharmacokinetics in relation to)

RN 437-38-7 ZCAPLUS

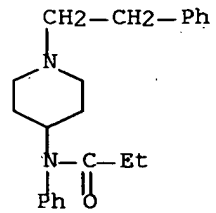
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



IT ***80430-19-9P***
RL: SPN (Synthetic preparation); ***PREP (Preparation)***
(preparation of)

RN 80430-19-9 ZCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, labeled with deuterium (9CI) (CA INDEX NAME)



L112 ANSWER 17 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:426431 HCAPLUS Full-text

DOCUMENT NUMBER: 147:78558

TITLE: Ultraperformance ***Liquid Chromatography***-Tandem Mass Spectrometry

Analysis of Stimulatory Drugs of Abuse in Wastewater and Surface Waters

AUTHOR(S): Huerta-Fontela, Maria; Galceran, Maria Teresa; Ventura, Francesc
CORPORATE SOURCE: AGBAR-Aiguees de Barcelona, Barcelona, 08018, Spain

SOURCE: Analytical Chemistry (Washington, DC, United States) (2007), 79(10), 3821-3829
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ultra-performance LC coupled with electro-spray tandem mass spectrometry was used for the rapid, simultaneous determination of 15 stimulatory drugs in water. Cocaine, amphetamine-related compds., lysergic acid diethylamide, ketamine, phencyclidine, fentanyl, and metabolites, among controlled drugs, and nicotine, caffeine, and their metabolites, among non-controlled drugs, were studied. Chromatog. ***separation*** was achieved in <4.5 min, with improved peak resolution and sensitivity. Compound identification and quantification was performed by selected reaction monitoring, using an electro-spray ionization source. Isotope dilution (except for paraxanthine) was used for quantitation. Method quality parameters were established and limits of quantification were obtained for controlled drugs in surface water at 0.1-3.1 ng/L and in wastewater at 0.2-4.0 ng/L. Run-to-run and day-to-day precision were evaluated in different water matrixes (Milli-Q water, surface water, wastewater). To assess the presence of these drugs in actual water samples, the optimized method was used to analyze wastewater and river water. Anal. of samples from wastewater treatment facilities in northeast Spain showed the presence of drugs, e.g., cocaine and amphetamine-related compds., in influent and effluent samples. Cocaine metabolites and MDMA (ecstasy) were also observed in surface water; nicotine and caffeine were detected in all analyzed samples. Results demonstrated the presence of these drugs in the aquatic media must be considered a matter of environmental concern.

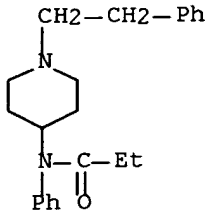
CC 61-3 (Water)
Section cross-reference(s): 60, 63, 80

IT 50-36-2, Cocaine 50-37-3, Lysergic acid diethylamide 54-11-5, Nicotine 58-08-2, Caffeine, analysis 77-10-1, Phencyclidine 300-62-9, 1-Phenylpropan-2-amine ***437-38-7***, Fentanyl 486-56-6, Cotinine 519-09-5 537-46-2, N-Methyl-1-phenylpropan-2-amine 611-59-6, Paraxanthine 1622-62-4, Flunitrazepam 4764-17-4, 3,4-Methylenedioxyamphetamine 6740-88-1, Ketamine 42542-10-9, 3,4-Methylenedioxymethamphetamine
RL: ANT (Analyte); OCU (Occurrence, unclassified); ANST (Analytical study); OCCU (Occurrence)
(stimulatory drug determination in water and wastewater by ultra-performance
LC-tandem mass spectrometry)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); OCU (Occurrence, unclassified); ANST (Analytical study); OCCU (Occurrence)
(stimulatory drug determination in water and wastewater by ultra-performance
LC-tandem mass spectrometry)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 18 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1298722 HCAPLUS Full-text
DOCUMENT NUMBER: 146:236313
TITLE: Characterization and comparison of the chromatographic performance of different types of reversed-phase stationary phases
AUTHOR(S): Stella, Cinzia; Rudaz, Serge; Gauvrit, Jean-Yves; Lanteri, Pierre; Huteau, Alban; Tchapla, Alain; Veuthey, Jean-Luc
CORPORATE SOURCE: Laboratory of Pharmaceutical Analytical Chemistry, School of Pharmaceutical Sciences, University of Geneva, Switz.
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2007), 43(1), 89-98
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The chromatog. performance of several base-deactivated stationary phases was evaluated with a specific chromatog. test. Seven basic test compds., possessing different physico-chemical properties were injected on different supports with two mobile phases: one at pH 7.0 (acetonitrile-phosphate buffer, 40:60, volume/volume), and the other at pH 3.0 (acetonitrile-phosphate buffer, 15:85, volume/volume). Chromatog. parameters obtained under these conditions were treated by principal component anal. (PCA) to ***sep*** . base deactivated supports according to their silanol activity (pH 7.0 mobile phase) and hydrophobic properties (pH 3.0 mobile phase). The information given by the specific test column evaluation was improved with complementary chemometric tools such as hierarchical cluster anal. The same base deactivated supports were also tested following a general test procedure issued from the literature and obtained fundamental properties (in particular silanol activity and hydrophobicity) were compared with column evaluation obtained with the specific test: results were in good agreement, although the use of the specific test offered a better differentiation between numerous base-deactivated supports.

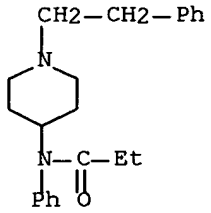
CC 64-1 (Pharmaceutical Analysis)
ST ***liq chromatog*** reversed stationary phase principal component analysis
IT ***HPLC***
Hydrophobicity
Principal component analysis
Reversed phase liquid chromatography
(characterization and comparison of chromatog. performance of different types of reversed-phase stationary phases)
IT 51-06-9, Procainamide 54-11-5, Nicotine 76-99-3, Methadone 110-86-1,

Pyridine, analysis 130-95-0, Quinine 133-16-4, Chloroprocaine
437-38-7, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(characterization and comparison of chromatog. performance of different types of reversed-phase stationary phases)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(characterization and comparison of chromatog. performance of different types of reversed-phase stationary phases)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

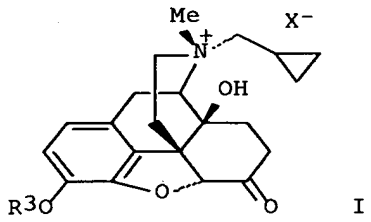
L112 ANSWER 19 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1252256 HCAPLUS Full-text
DOCUMENT NUMBER: 146:27970
TITLE: Synthesis of (17R)-N-methylnaltrexones for use in pharmaceutical compositions for the treatment of gastrointestinal disorders
INVENTOR(S): Doshan, Harold D.; Perez, Julio
PATENT ASSIGNEE(S): Progenics Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 94pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006127899	A2	20061130	WO 2006-US20233	20060525
WO 2006127899	A3	20070208		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2007099946 A1 20070503 US 2006-441395 20060525
PRIORITY APPLN. INFO.: US 2005-684616P P 20050525
OTHER SOURCE(S): CASREACT 146:27970; MARPAT 146:27970
GI



I

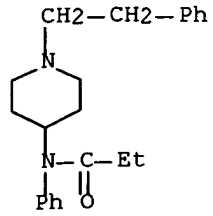
AB (17R)-N-Methylnaltrexones (R-MNTX), such as I (R3 = H; X = halide, sulfate, phosphate, nitrate, etc.), were stereoselectively prepared for use in pharmaceutical compns. useful for the treatment of gastrointestinal disorders. Thus, (17R)-N-Methylnaltrexone bromide I (R3 = H, X = Br) was enantioselectively prepared via esterification of naltrexone with Me2CCOCl, stereoselective methylation of the resulting 3-O-isobutyrylnaltrexone with MeI, acid hydrolysis with HBr of the resulting O-acylated iodide I (R3 = COCHMe2, X = iodo) and subsequent ***purification*** using ***HPLC*** to obtain the target bromide. Pharmaceutical formulation of the I (R3 = H, X = Br) were presented.

CC 31-3 (Alkaloids)
Section cross-reference(s): 1, 63

IT 57-27-2, Morphine, biological studies 57-42-1, Meperidine 62-67-9, Nalorphine 69-65-8, Mannitol 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 89-57-6, Mesalamine 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 144-14-9, Anileridine 152-02-3, Levallorphan 359-83-1, Pentazocine ***437-38-7***, Fentanyl 446-86-6, Azothioprine 466-99-9, Hydromorphone 469-62-5, Propoxyphene 561-27-3, Diacetylmorphine 599-79-1, Sulfasalazine 1477-40-3, Levomethadyl acetate 15686-91-6, Propiram 15722-48-2, Olsalazine 20594-83-6, Nalbuphine 27203-92-5, Tramadol 39133-31-8, Trimebutine 42408-82-2, Butorphanol 51931-66-9, Tilidine 53179-11-6, Loperamide 53648-55-8, Dezocine 56030-54-7 71195-58-9, Alfentanyl 75684-07-0, Bremazocine 104987-11-3, Tacrolimus 123618-00-8, Fedotozine 132875-61-7, Remifentanyl 152923-56-3, Daclizumab 170277-31-3, Infliximab 179045-86-4, Basiliximab
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy agent; asym. synthesis of (17R)-N-methylnaltrexones for use in pharmaceutical compns. for treatment of gastrointestinal disorders)

IT ***437-38-7***, Fentanyl
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy agent; asym. synthesis of (17R)-N-methylnaltrexones for use in pharmaceutical compns. for treatment of gastrointestinal disorders)

RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 20 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1252272 HCAPLUS Full-text
DOCUMENT NUMBER: 146:27967
TITLE: Preparation of (S)-N-methylnaltrexones with opioid receptor binding activity for use in pharmaceutical compositions
INVENTOR(S): Wagoner, Howard; Sanghvi, Suketu P.; Boyd, Thomas A.; Verbicky, Christopher; Andruski, Stephen
PATENT ASSIGNEE(S): Progenics Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 102pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006127898	A2	20061130	WO 2006-US20232	20060525
WO 2006127898	A3	20070208		
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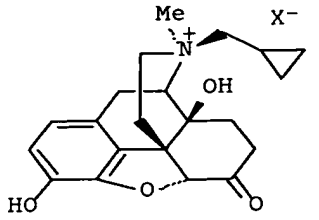
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2007265293	A1	20071115	US 2006-441452	20060525

PRIORITY APPLN. INFO.: US 2005-684570P P 20050525
OTHER SOURCE(S): MARPAT 146:27967
GI



I

AB (17S)-N-methylnaltrexones (S-MNTX), such as I [X = halogen, nitrate, sulfate, phosphate], were prepared as opioid receptor agonists for therapeutic use in the treatment of pain diarrhea, inflammation and central nervous system disorders and for use in combination with other therapeutic agents. Thus, (17S)-N-methylnaltrexone bromide I (X = Br) was stereoselectively prepared via an alkylation reaction of oxymorphone with iodomethylcyclopropane using NMP and pieces of copper wire to form the corresponding iodide I (X = iodo) and subsequent ion exchange and ***purification*** by ***HPLC*** to give the target bromide with 95% purity. I (X = Br) was assayed for opioid receptor binding with binding activity shown for the μ- and κ-receptors and no binding with δ-receptors. Addnl. pharmacol. testing included antidiarrheal and analgesic activity.

CC 31-1 (Alkaloids)
Section cross-reference(s): 1, 63

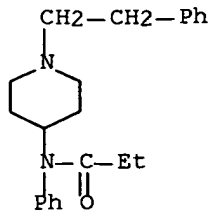
IT 51-55-8, Atropine, biological studies 57-27-2, Morphine, biological studies 57-42-1, Meperidine 57-67-0, Sulfaguanidine 62-67-9, Nalorphine 67-45-8, Furazolidone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 85-73-4, Phthalylsulfathiazole 89-57-6, Mesalamine 99-26-3, Bismuth subgallate 101-31-5, Hyoscyamine 116-43-8, Succinylsulfathiazole 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 144-14-9, Anileridine 152-02-3, Levallorphan 359-83-1, Pentazocine ***437-38-7***, Fentanyl 446-86-6, Azothioprine 466-99-9, Hydromorphone 469-62-5, Propoxyphene 546-93-0, Magnesium carbonate 561-27-3, Diacetylmorphine 599-79-1, Sulfasalazine 813-93-4, Bismuth citrate 915-30-0, Diphenoxylate 1304-85-4, Bismuth subnitrate 1309-42-8, Magnesium hydroxide 1327-43-1, Magnesium aluminum silicate 1477-40-3, Levomethadyl acetate 5892-10-4, Bismuth subcarbonate 6591-56-6, Bismuth tartrate 9000-69-5, Pectin 12250-51-0, Bismuth aluminate 14882-18-9, Bismuth subsalicylate 15686-91-6, Propiram 15722-48-2, Olsalazine 20290-10-2, Morphine-6-glucuronide 20594-83-6, Nalbuphine 21645-51-2, Aluminum hydroxide, biological studies 27203-92-5, Tramadol 28782-42-5, Difenoxin 39133-31-8, Trimebutine 42408-82-2, Butorphanol 51931-66-9, Tilidine 53179-11-6, Loperamide 53648-55-8, Dezocine 56030-54-7 57644-54-9, Bismuth subcitrate 71195-58-9, Alfentanyl 75684-07-0, Bremazocine 81098-60-4, Cisapride 83150-76-9, Octreotide 103577-45-3, Lansoprazole 104987-11-3, Tacrolimus 123618-00-8, Fedotozine 132875-61-7, Remifentanyl 152923-56-3, Daclizumab 153205-46-0, Asimadoline 170277-31-3, Infliximab 179045-86-4, Basiliximab
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(claimed combination therapy agent; preparation of (17S)-N-methylnaltrexones
with opioid receptor binding activity for therapeutic use in the treatment of central nervous system disorders and diarrhea)

IT ***437-38-7***, Fentanyl
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(claimed combination therapy agent; preparation of (17S)-N-methylnaltrexones
with opioid receptor binding activity for therapeutic use in the treatment of central nervous system disorders and diarrhea)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 21 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:704513 HCAPLUS Full-text

DOCUMENT NUMBER: 145:224260

TITLE: An automated and fully validated LC-MS/MS procedure for the simultaneous determination of 11 opioids used in palliative care, with 5 of their metabolites

AUTHOR(S): Musshoff, F.; Trafkowski, J.; Kuepper, U.; Madea, B.

CORPORATE SOURCE: Institute of Forensic Medicine, Bonn, 53111, Germany

SOURCE: Journal of Mass Spectrometry (2006), 41(5), 633-640
CODEN: JMSPFJ; ISSN: 1076-5174

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A fully validated ***liquid chromatog.*** procedure coupled with electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) is presented for quant. determination of the opioids buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, piritramide, tilidine, and tramadol together with their metabolites bisnortilidine, morphine-glucuronides, norfentanyl, and nortilidine in blood plasma after an automatically performed solid-phase extraction (SPE). ***Separation*** was achieved in 35 min on a Phenomenex C12 MAX-RP column (4 μm, 150 + 2 mm) using a gradient of ammonium formiate buffer (pH 3.5) and acetonitrile. The validation data were within the required limits. The assay was successfully applied to authentic plasma samples, allowing confirmation of the diagnosis of overdose situations as well as monitoring of patients' compliance, especially in patients under palliative care.

CC 1-1 (Pharmacology)
Section cross-reference(s): 4

ST opioid detn ***sepn HPLC*** mass spectrometry blood analysis forensic

IT Tandem mass spectrometry
(***HPLC***, combined with; LC-MS/MS simultaneous determination of opioids used in palliative care)

IT Resolution (***separation***)
(chromatog.; LC-MS/MS simultaneous determination of opioids used in palliative care)

IT ***HPLC***

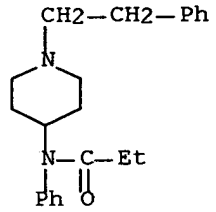
(combined with tandem mass spectrometry; LC-MS/MS simultaneous determination of
opioids used in palliative care)

IT 57-27-2, Morphine, biological studies 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 302-41-0, Piritramide ***437-38-7***, Fentanyl 466-99-9, Hydromorphone 1609-66-1, Norfentanyl 20290-10-2, Morphine-glucuronide 27203-92-5, Tramadol 38677-94-0, Nortilidine 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53948-51-9, Bisnortilidine
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(LC-MS/MS simultaneous determination of opioids used in palliative care)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(LC-MS/MS simultaneous determination of opioids used in palliative care)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 22 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1139999 HCAPLUS Full-text

DOCUMENT NUMBER: 146:92543

TITLE: New screening method for basic compounds in urine by on-line extraction-high-performance ***liquid chromatography*** with photodiode-array detection

AUTHOR(S): Schoenberg, Lena; Grobosch, Thomas; Lampe, Dagmar; Kloft, Charlotte

CORPORATE SOURCE: Berliner Betrieb fuer Zentrale Gesundheitliche Aufgaben (BBGes), Institute of Clinical Toxicology-Clinical Toxicology and Poison Control Center, Oranienburgerstrasse 285, Berlin, 13437, Germany

SOURCE: Journal of Chromatography, A (2006), 1134(1-2), 177-185
CODEN: JCRAEY; ISSN: 0021-9673

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A fully automated, qual. screening ***HPLC*** method for the identification of basic compds. in urine has been developed. A 1-mL volume of urine was extracted by online extraction and ***separated*** on two coupled strong cation-exchange (SCX) columns (2 + LunaSCX, 150 mm + 4.6 mm, 5 μm) under isocratic conditions. The mobile phase consisted of a mixture of potassium dihydrogenphosphate buffer

(pH 2.3) and acetonitrile. The use of photodiode-array detection (DAD, λ = 190-800 nm) gave access to a library of approx. 2600 toxicol. relevant compds. The validated method is reliable, simple and in addition successfully proven with the anal. of real biol. specimen for the routine use.

CC 1-1 (Pharmacology)
Section cross-reference(s): 4

ST urine screening basic compd online extn ***HPLC*** photodiode detection

IT Polymers, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(-based carboxylic or benzenesulfonic acid function; new screening method for basic compds. in urine by online extraction-high-performance ***liquid chromatog.*** with photodiode-array detection)

IT Drugs of abuse
(abuse of; basic compound screening in urine by online extraction-***HPLC*** with photodiode-array detection)

IT Photodiodes
(detection; new screening method for basic compds. in urine by online extraction-high-performance ***liquid chromatog.*** with photodiode-array detection)

IT Forensic analysis
(drug; new screening method for basic compds. in urine by online extraction-
HPLC with photodiode-array detection)

IT ***Cation exchange HPLC***
Urine
(new screening method for basic compds. in urine by online extraction-high-performance ***liquid chromatog.*** with photodiode-array detection)

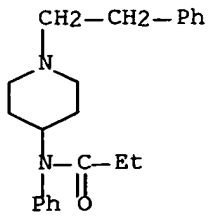
IT 7631-86-9, Silica, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(-based carboxylic or benzenesulfonic acid function; new screening method for basic compds. in urine by online extraction-high-performance ***liquid chromatog.*** with photodiode-array detection)

IT 50-36-2, Cocaine 51-34-3, Scopolamine 51-55-8, Atropine, analysis 57-27-2, Morphine, analysis 57-42-1, Pethidine 76-42-6, Oxycodone 76-57-3, Codeine 114-80-7, Neostigmine bromide 299-42-3, Ephedrine 300-62-9, Amphetamine ***437-38-7***, Fentanyl 467-15-2, Norcodeine 519-09-5, Benzoylecgonine 520-53-6, Psilocine 537-46-2, Methamphetamine 561-27-3, Heroin 2784-73-8, 6-Acetylmorphine 4764-17-4, Methylenedioxyamphetamine 27203-92-5, Tramadol 30223-73-5, EDDP 38677-94-0, Nortilidine 42542-10-9, Methylenedioxymethamphetamine 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53948-51-9, Bisnortilidine 78715-23-8, Norbuprenorphine
RL: ANT (Analyte); ANST (Analytical study)
(new screening method for basic compds. in urine by online extraction-high-performance ***liquid chromatog.*** with photodiode-array detection)

IT 98-11-3D, Benzenesulfonic acid, polymeric derivs. 100-42-5D, Styrene, divinylbenzene/methacrylate copolymer 1321-74-0D, Divinylbenzene, styrene/methacrylate copolymer 9003-70-7, Polystyrene-divinylbenzene 9058-17-7
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(new screening method for basic compds. in urine by online extraction-high-performance ***liquid chromatog.*** with photodiode-array detection)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(new screening method for basic compds. in urine by online extraction-high-performance ***liquid chromatog.*** with

photodiode-array detection)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 23 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:452736 HCAPLUS Full-text
DOCUMENT NUMBER: 145:97622
TITLE: Screening for basic drugs in equine urine using direct-injection differential-gradient LC-LC coupled to hybrid tandem MS/MS
AUTHOR(S): Stanley, Shawn M. R.; Foo, Hsiao Ching
CORPORATE SOURCE: Singapore Race Course, The Singapore Turf Club Laboratory, Singapore, 738078, Singapore
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2006), 836(1-2), 1-14
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid, selective and robust direct-injection LC/hybrid tandem MS method has been developed for simultaneous screening of more than 250 basic drugs in the supernatant of enzyme hydrolyzed equine urine. Analytes, trapped using a short HLB extraction column, are refocused and ***separated*** on a Sunfire C18 anal. column using a controlled differential gradient generated by proportional dilution of the first column's eluent with water. Independent data acquisition (IDA) was configured to trigger a sensitive enhanced product ion (EPI) scan when a multiple reaction monitoring (MRM) survey scan signal exceeded the defined criteria. The decision on whether or not to report a sample as a pos. result was based upon both the presence of a MRM response within the correct retention time range and a qual. match between the EPI spectrum obtained and the corresponding reference standard Ninety seven percent of the drugs targeted by this method met our detection criteria when spiked into urine at 100 ng/mL; 199 were found at 10 ng/mL, 83 at 1 ng/mL and 4 at 0.1 ng/mL.
CC 4-2 (Toxicology)
Section cross-reference(s): 1
IT Drugs of abuse
Equus caballus
Liquid chromatography
Tandem mass spectrometry
Urine analysis
(screening for basic drugs in equine urine using direct-injection

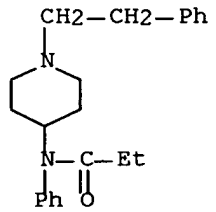
differential-gradient LC-LC coupled to hybrid tandem MS/MS)

IT 50-37-3, Lysergic acid diethylamide 50-47-5, Desipramine 50-49-7, Imipramine 50-55-5, Reserpine 51-34-3, Hyoscine 52-53-9, Verapamil 52-86-8, Haloperidol 54-11-5, Nicotine 56-94-0, Demecarium bromide 57-42-1, Pethidine 58-00-4, Apomorphine 58-08-2, Caffeine, analysis 58-25-3, Chlorodiazepoxide 58-32-2, Dipyridamol 58-38-8 58-39-9, Perphenazine 58-40-2, Promazine 58-73-1, Diphenhydramine 59-26-7, Nikethamide 59-46-1, Procaine 59-63-2, Isocarboxazide 60-80-0, Phenazone 60-87-7, Promethazine 60-99-1, Methotrimeprazine 61-00-7, Acepromazine 62-67-9, Nalorphine 64-77-7, Tolbutamide 64-95-9, Adiphenine 68-88-2, Hydroxyzine 69-23-8, Fluphenazine 70-07-5, Mephenoxalone 72-44-6, Methaqualone 72-69-5, Nortriptyline 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-10-1, Phencyclidine 77-20-3, Alphaprodine 77-37-2, Procyclidine 80-50-2, Anisotropine methyl bromide 83-98-7, Orphenadrine 85-79-0, Dibucaine 86-13-5, Benztropine 86-54-4, Hydralazine 90-84-6, Diethylpropion 91-81-6 93-30-1, Methoxyphenamine 94-09-7, Benzocaine 94-24-6, Tetracaine 94-25-7, Butamben 96-88-8, Mepivacaine 100-92-5, Mephentermine 101-31-5, Hyoscyamine 103-86-6, Hydroxyamphetamine 113-59-7, Chlorprothixene 117-89-5, Trifluoperazine 125-28-0, Dihydrocodeine 125-71-3, Dextromethorphan 125-73-5, Dextrorphan 132-22-9, Chloropheniramine 134-49-6, Phenmetrazine 137-58-6, Lidocaine 144-11-6 144-14-9, Anileridine 146-22-5, Nitrazepam 146-48-5, Yohimbine 149-16-6, Butacaine 156-08-1, Benzphetamine 298-46-4, Carbamazepine 298-50-0, Propantheline 298-57-7, Cinnarizine 299-42-3, Ephedrine 300-62-9, Amphetamine 302-33-0, Proadifen 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 309-29-5, Doxapram 359-83-1, Pentazocine 361-37-5 370-14-9 395-28-8, Isoxsuprine ***437-38-7***, Fentanyl 438-60-8, Protriptyline 439-14-5, Diazepam 442-52-4, Clemizole 447-41-6, Nylidrin 458-24-2, Fenfluramine 465-65-6, Naloxone 469-21-6, Doxylamine 476-70-0, Boldine 479-18-5, Diphylline 480-30-8, Dichloralphenazone 485-71-2, Cinchonidine 486-56-6, Cotinine 495-70-5, Meprylcaine 499-67-2, Proparacaine 514-65-8, Biperiden 519-09-5, Benzoylecgonine 522-00-9, Ethopropazine 525-66-6, Propranolol 530-08-5, Isoetharine 532-03-6, Methocarbamol 532-77-4, Hexylcaine 541-22-0, Decamethonium bromide 548-73-2, Droperidol 554-57-4, Methazolamide 586-06-1, Metaproterenol 596-51-0, Glycopyrrolate 604-75-1, Oxazepam 634-03-7, Phendimetrazine 636-54-4, Clopamide 642-72-8, Benzydamine 657-24-9, 1,1-Dimethylbiguanide 695-34-1, 2-Amino-4-picoline 721-50-6, Prilocaine 739-71-9, Trimipramine 846-49-1, Lorazepam 846-50-4, Temazepam 848-75-9 915-30-0, Diphenoxylate 1088-11-5, Nordiazepam 1134-47-0, Baclofen 1622-61-3, Clonazepam 1668-19-5, Doxepin 1812-30-2, Bromazepam 1977-10-2, Loxapine 1982-37-2, Methdilazine 2139-47-1, Nifenazone 2609-46-3, Amiloride 2804-05-9, Azaperol 2894-67-9, Delorazepam 2955-38-6, Prazepam 3568-24-9, Propionylpromazine 3572-43-8 3605-01-4, Piribedil 3820-67-5, Glafenine 4093-35-0, Bromopride 4764-17-4, 3,4-Methylenedioxyamphetamine 5051-62-7, Guanabenz 5053-06-5, Fenspiride 5370-01-4 5633-20-5, Oxybutynin 5786-21-0, Clozapine 6493-05-6, Pentoxifylline 6740-88-1, Ketamine 7020-55-5, Clidinium 7361-61-7, Xylazine 7492-32-2, Isopropamide 7640-51-9, Promethazine sulfoxide 7683-59-2, Isoprenaline 10238-21-8, Glibenclamide 10262-69-8, Maprotiline 13364-32-4, Clobenzorex 13392-18-2, Fenoterol 13473-38-6, Pipenzolate 13523-86-9, Pindolol 13655-52-2, Alprenolol 14028-44-5, Amoxapine 14116-06-4, 4-Methylthioamphetamine 14214-84-7, Oxyphenonium 14357-78-9, Diprenorphine 14611-51-9, Selegiline 14838-15-4, Norephedrine 15500-66-0, Pancuronium 15588-95-1, 4-Methyl-2,5-dimethoxyamphetamine 15676-16-1, Sulpiride 15687-14-6, Embutramide 17617-23-1, Flurazepam 17692-51-2, Metergoline

18559-94-9, Salbutamol 18683-91-5, Ambroxol 20566-69-2, Dimidium
20594-83-6, Nalbuphine 21187-98-4, Gliclazide 21256-18-8, Oxaprozin
22316-47-8, Clobazam 23092-17-3, Halazepam 25614-03-3, Bromocriptine
25905-77-5, Minaprine 25990-43-6, Mepenzolate 26171-23-3, Tolmetin
26839-75-8, Timolol 27203-92-5, Tramadol 27470-51-5, Suxibuzone
28981-97-7, Alprazolam 29094-61-9, Glipizide 29975-16-4, Estazolam
31842-01-0, Indoprofen 33369-31-2, Zomepirac 34368-04-2, Dobutamine
34552-84-6, Isoxicam 34580-13-7, Ketotifen 34911-55-2, Bupropion
36322-90-4, Piroxicam 36735-22-5, Quazepam 37115-43-8 37115-45-0
37148-27-9, Clenbuterol 37517-30-9, Acebutolol 38396-39-3, Bupivacaine
42399-41-7 42924-53-8, Nabumetone 43200-80-2, Zopiclone 50679-08-8,
Terfenadine 51152-91-1, Butaclamol 51481-61-9, Cimetidine
53772-83-1, Zuclopenthixol 54063-53-5, Propafenone 54739-18-3,
Fluvoxamine 55837-25-7, Buflomedil 55985-32-5, Nicardipine
56030-54-7 57808-66-9, Domperidone 59467-70-8, Midazolam 59729-33-8,
Citalopram 60142-96-3, Gabapentin 60205-81-4, Ipratropium 63590-64-7
63659-18-7, Betaxolol 64228-79-1, Atracurium 64840-90-0, Eperisone
65896-16-4, Romifidine 66357-35-5, Ranitidine 66722-44-9, Bisoprolol
68693-11-8, Modafinil 68767-14-6, Loxoprofen 71031-15-7, Cathinone
71195-58-9, Alfentanyl 71320-77-9, Moclobemide 72797-41-2, Tianeptine
72895-88-6, Eltenac 73644-42-5, 2-(1-Hydroxyethyl)promazinesulfoxide
76631-46-4, Detomidine 76824-35-6, Famotidine 79617-96-2, Sertraline
82801-81-8 82834-16-0, Perindopril 83200-09-3, Dembrexine
RL: ANT (Analyte); ANST (Analytical study)
(screening for basic drugs in equine urine using direct-injection differential-gradient LC-LC coupled to hybrid tandem MS/MS)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(screening for basic drugs in equine urine using direct-injection differential-gradient LC-LC coupled to hybrid tandem MS/MS)

RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 24 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:366570 HCAPLUS Full-text
DOCUMENT NUMBER: 143:247
TITLE: Determination of fentanyl in human plasma and fentanyl and norfentanyl in human urine using LC-MS/MS
AUTHOR(S): Huynh, N.-H.; Tyrefors, N.; Ekman, L.; Johansson, M.
CORPORATE SOURCE: Analytical Services, Quintiles AB, Uppsala, SE 75323, Swed.
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2005), 37(5), 1095-1100

CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fentanyl, a potent analgesic drug, has traditionally been used i.v. in surgical or diagnostic operations. Formulations with fentanyl in oral transmucosal delivery system and in transdermal depot-patch were also developed against breakthrough pain in cancer patients. In this report, LC-MS/MS methods to determine fentanyl in human blood plasma as well as fentanyl and its main metabolite, norfentanyl, in human urine are presented together with validation data. The validation ranges were 0.020-10.0 and 0.100-50.0 ng/mL for fentanyl in plasma and urine, resp., and 0.102-153 ng/mL for norfentanyl in urine. Liquid-liquid extraction of the compds. fentanyl, norfentanyl and the deuterated internal stds., fentanyl-d5 and norfentanyl-d5 from the matrixes was applied and ***separation*** was performed on a reversed phase YMC Pro C18-column followed by MS/MS detection with electrospray in pos. mode. The inter-assay precision (CV%) was better than 4.8% for fentanyl in plasma and 6.2% and 4.7% for fentanyl and norfentanyl, resp., in urine. The ruggedness of the methods, selectivity, recovery, effect of dilution and long-term stability of the analytes in plasma and urine were investigated. Effect of hemolysis and stability of fentanyl in blood samples were also studied. The methods were applied for the determination of fentanyl in plasma samples and fentanyl/norfentanyl in urine samples taken for pharmacokinetic evaluation after a single i.v. dose of 75 μg fentanyl.

CC 1-1 (Pharmacology)

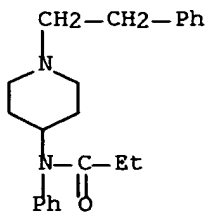
IT Analgesics
Blood analysis
Human
Liquid chromatography
Tandem mass spectrometry
Urine analysis
(determination of fentanyl in human blood plasma and fentanyl and norfentanyl
in human urine using LC-MS/MS)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); PKT (Pharmacokinetics); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(determination of fentanyl in human blood plasma and fentanyl and norfentanyl
in human urine using LC-MS/MS)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); PKT (Pharmacokinetics); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(determination of fentanyl in human blood plasma and fentanyl and norfentanyl
in human urine using LC-MS/MS)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 25 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1142217 HCAPLUS Full-text
DOCUMENT NUMBER: 143:447008
TITLE: A rapid ***HPLC*** procedure for analysis of analgesic pharmaceutical mixtures for quality assurance and drug diversion testing
AUTHOR(S): Wolf, Carl E.; Poklis, Alphonse
CORPORATE SOURCE: Department of Pathology, Virginia Commonwealth University School of Medicine, Richmond, VA, 23298-0165, USA
SOURCE: Journal of Analytical Toxicology (2005), 29(7), 711-714
CODEN: JATOD3; ISSN: 0146-4760
PUBLISHER: Preston Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A simple high-performance ***liquid chromatog.*** (***HPLC***) method that allows for the rapid identification and quantification of analgesic and anesthetic solns. typically used in surgical procedures or patient controlled analgesia is presented. The ***separation*** of bupivacaine, clonidine, fentanyl, hydromorphone, midazolam, and morphine is complete in < 20 min. The method allows test solns. to be either directly injected or diluted prior to injection into the ***HPLC*** system. The method is useful from the standpoint that pharmaceutical prepns. are usually submitted with the known drug of interest and expected concentration The method is also useful for initial screening of solns. submitted that are either unknown or of questionable identity. The method was successfully applied as part of hospital-based quality control and quality assurance programs to detect not only errors in the preparation of solns. of scheduled drugs, but also to uncover illegal diversion of drugs of abuse by medical personnel. (c) 2005 Preston Publications.

CC 64-3 (Pharmaceutical Analysis)
Section cross-reference(s): 4

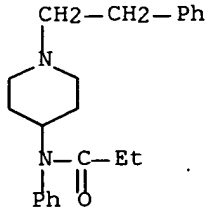
ST analgesic pharmaceutical detn ***HPLC*** quality drug diversion

IT Analgesics
Anesthetics
Drugs of abuse
HPLC
Human
Quality control
(***HPLC*** anal. of analgesic pharmaceutical mixts. for quality assurance and drug diversion testing)

IT 57-27-2, Morphine, analysis ***437-38-7***, Fentanyl 466-99-9, Hydromorphone 4205-90-7, Clonidine 38396-39-3, Bupivacaine 59467-70-8, Midazolam
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(***HPLC*** anal. of analgesic pharmaceutical mixts. for quality assurance and drug diversion testing)

IT ***437-38-7***, Fentanyl
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(***HPLC*** anal. of analgesic pharmaceutical mixts. for quality

assurance and drug diversion testing)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 26 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:217334 HCAPLUS Full-text
DOCUMENT NUMBER: 142:475225
TITLE: Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: A new approach to treatment of incident pain
AUTHOR(S): Lennernaes, B.; Hedner, T.; Holmberg, M.; Bredenberg, S.; Nystroem, C.; Lennernaes, H.
CORPORATE SOURCE: Department of Oncology, Karolinska Hospital, Stockholm, Swed.
SOURCE: British Journal of Clinical Pharmacology (2005), 59(2), 249-253
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aims: It is estimated that two-thirds of cancer patients will at some point during their illness experience breakthrough pain. In this study, the pharmacokinetics of a novel sublingual dosage form of fentanyl developed for breakthrough pain was evaluated. Methods: Eleven Caucasian patients (seven male and 4 female, aged 34-75 years, median 60 years) with metastatic malignant disease were recruited initially, but three patients withdrew. Prior to the study all patients were on continuous nonfentanyl opiate medication. The study was a double-blind, cross-over trial, consisting of three 1-day treatment periods. A new rapidly dissolving preparation of fentanyl, was administered sublingually in single doses of 100, 200 and 400 μg, resp., on three ***sep***. occasions. Plasma fentanyl concns. were determined using ***liquid chromatog***.-mass spectrometry/mass spectrometry (LC-MS/MS). Pharmacokinetic parameters were calculated by noncompartment anal. Tolerability and the occurrence of adverse events were monitored throughout the study by patient questionnaire. Results: The data from nine subjects who completed at least two periods were used in the anal. of variance. There were no significant differences between doses (100, 200 and 400 μg) for dose adjusted AUC ($F = 0.42$, $P = 0.6660$), dose adjusted Cmax ($F = 0.08$, $P = 0.9206$) and Tmax ($F = 0.94$, $P = 0.4107$). Thus, these parameters showed dose proportionality. The differences (400-100μg) in dose adjusted AUC from the three-period crossover anal. was -0.016 min·ng/mL ($t = 0.71$, $P = 0.8718$). Interindividual variability in systemic exposure to fentanyl was fairly small

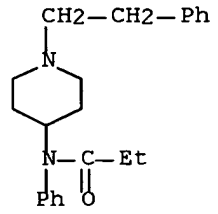
(25-40%), which may be related to a good in vivo biopharmaceutical performance of the sublingual tablet, and a relatively small fraction of the dose being swallowed. The first detectable plasma concentration of fentanyl was observed between 8 and 11 min after administration. Tmax increased from 39.7 ± 17.4 to 48.7 ± 26.3 and 56.7 ± 24.6 min for the 100, 200 and 400 μg doses, resp. Adverse events were few and did not increase with increasing dose. Conclusion: With this rapidly dissolving fentanyl formulation, the first detectable plasma concentration of fentanyl was observed at 8-11 min after administration. The pharmacokinetics of the drug showed dose proportionately. This formulation of fentanyl seemed to be well tolerated by the patients.

CC 1-2 (Pharmacology)
Section cross-reference(s): 63

IT ***437-38-7,*** Fentanyl
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sublingual administration of μ-opioid receptor agonist fentanyl was well tolerated with dose-dependent pharmacokinetics and small interindividual variability for treatment of pain in Caucasian population with metastatic malignant disease)

IT ***437-38-7,*** Fentanyl
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sublingual administration of μ-opioid receptor agonist fentanyl was well tolerated with dose-dependent pharmacokinetics and small interindividual variability for treatment of pain in Caucasian population with metastatic malignant disease)

RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 27 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1302038 HCAPLUS Full-text
DOCUMENT NUMBER: 144:144397
TITLE: High-performance ***liquid chromatography*** of seized drugs at elevated pressure with 1.7μm hybrid C18 stationary phase columns
AUTHOR(S): Lurie, Ira S.
CORPORATE SOURCE: Special Testing and Research Laboratory, US Drug Enforcement Administration, Dulles, VA, 20166, USA
SOURCE: Journal of Chromatography, A (2005), 1100(2), 168-175
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB High-performance ***liquid chromatog.*** (***HPLC***) ***separation*** of drugs at elevated pressure with 1.7 μm hybrid C18 stationary phase columns was investigated. This technique, which uses instrumentation engineered to handle the narrow peaks and high back pressures generated by 1.7 μm particle columns, provided significantly better resolution and/or faster anal. than conventional ***HPLC*** and capillary electrophoresis (CE). The use of 2 mm internal diameter (i.d.) columns of 3-10 cm length has been evaluated for the ***separation*** of basic and neutral drugs, drug profiling, and general screening (including acidic drugs). For these applications, compared to conventional ***HPLC*** and CE, it provided up to 12+ and 3+ faster analyses, resp. Precision was excellent for both isocratic and gradient analyses. For retention time and peak area, RSDs of ≤0.1% were obtainable. Fifteen anabolic steroids and esters were well ***sepd*** . in a 2.5 min gradient. For drug profiling, compared to ***HPLC*** and CE, approx. twice as many peaks were resolved. ***HPLC*** at elevated pressure is also well suited as a general screening technique. Twenty-four solutes of varying drug classes including narcotic analgesics, stimulants, depressants, hallucinogens, and anabolic steroids were fully ***separated*** in a 13.5 min gradient.

CC 4-2 (Toxicology)
Section cross-reference(s): 1

ST forensic ***HPLC*** drug abuse screening

IT Hormones, animal, analysis
RL: ANT (Analyte); ANST (Analytical study)
(anabolic steroids; high-performance ***liquid chromatog*** . of seized drugs at elevated pressure with 1.7μm hybrid C18 stationary phase columns)

IT Forensic analysis
(drug; high-performance ***liquid chromatog.*** of seized drugs at elevated pressure with 1.7μm hybrid C18 stationary phase columns)

IT Drug screening
Drugs of abuse
HPLC
Narcotics
Nervous system stimulants
Psychotomimetics
(high-performance ***liquid chromatog.*** of seized drugs at elevated pressure with 1.7μm hybrid C18 stationary phase columns)

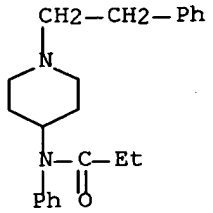
IT 50-06-6, Phenobarbital, analysis 50-36-2, Cocaine 50-37-3, LSD 57-27-2, Morphine, analysis 57-85-2, Testosterone propionate 58-18-4, Methyltestosterone 58-20-8, Testosterone cypionate 58-22-0, Testosterone 62-90-8, Nandrolone phenylpropionate 72-44-6, Methaqualone 72-63-9, Methandrostenolone 76-43-7, Fluoxymesterone 76-57-3, Codeine 77-10-1, PCP 300-62-9, Amphetamine 315-37-7, Testosterone enanthate 360-70-3, Nandrolone decanoate 434-22-0, Nandrolone ***437-38-7***, Fentanyl 438-41-5, Librium 439-14-5, Diazepam 520-52-5, Psilocybin 520-53-6, Psilocin 521-10-8, Methandriol 521-18-6, Stanolone 537-46-2, Methamphetamine 561-27-3, Heroin 846-48-0, Boldenone 846-49-1, Lorazepam 855-19-6, Clostebol acetate 1045-69-8, Testosterone acetate 1169-49-9, Testosterone isobutyrate 1972-08-3, Δ9-THC 2363-59-9 3593-85-9, Methandriol dipropionate 4764-17-4, MDA 5721-91-5, Testosterone decanoate 5949-44-0, Testosterone undecanoate 7207-92-3, Nandrolone propionate 10418-03-8, Stanozolol 13103-34-9, Boldenone undecylenate 13956-29-1, Cannabidiol 15262-86-9, Testosterone isocaproate 17230-88-5, Danazol 33854-98-7 42542-10-9, 3,4-Methylenedioxymethamphetamine 82801-81-8, 3,4-Methylenedioxyethylamphetamine
RL: ANT (Analyte); ANST (Analytical study)
(high-performance ***liquid chromatog.*** of seized drugs

at elevated pressure with 1.7μm hybrid C18 stationary phase columns)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(high-performance ***liquid chromatog.*** of seized drugs
at elevated pressure with 1.7μm hybrid C18 stationary phase columns)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 28 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:679329 HCAPLUS Full-text

DOCUMENT NUMBER: 142:169736

TITLE: Xenon Improves Recovery from Myocardial Stunning in Chronically Instrumented Dogs

AUTHOR(S): Grosse Hartlage, Maike A.; Berendes, Elmar; Van Aken, Hugo; Fobker, Manfred; Theisen, Marc; Weber, Thomas P.

CORPORATE SOURCE: Department of Anaesthesiology and Intensive Care, University Hospital Muenster, Muenster, Germany

SOURCE: Anesthesia & Analgesia (Hagerstown, MD, United States) (2004), 99(3), 655-664
CODEN: AACRAT; ISSN: 0003-2999

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In this study we tested the hypothesis that inhalational administration of xenon improves recovery from myocardial stunning. Ten dogs were chronically instrumented for measurement of heart rate; left atrial, aortic, and left ventricular pressure; coronary blood-flow velocity; and myocardial wall-thickening fraction. Regional myocardial blood flow was determined with fluorescent microspheres. Catecholamine plasma levels were measured by high-performance ***liquid chromatog.*** An occluder around the left anterior descending artery (LAD) allowed the induction of a reversible LAD ischemia. Animals underwent 2 exptl. conditions in a randomized crossover fashion on ***sep.*** days: (a) 10 min of LAD occlusion under fentanyl (25 μg · kg · h) and midazolam (0.6 mg · kg · h) (control) and (b) a second ischemic episode under the same basal anesthesia with concomitant inhalational administration of 75 ± 1 vol% xenon (intervention). Anesthesia was induced 35 min before LAD occlusion and was discontinued after 20 min of reperfusion. Dogs receiving xenon showed a significantly better recovery of wall-thickening fraction up to 12 h after ischemia. The increase in plasma epinephrine during emergence from anesthesia and in the early reperfusion period was significantly attenuated in the xenon group. There were no differences between groups concerning global hemodynamics, blood-flow velocity, or regional myocardial blood flow. In conclusion, inhalational administration of 75 vol% xenon improves recovery

from myocardial stunning in chronically instrumented dogs under fentanyl/midazolam anesthesia.

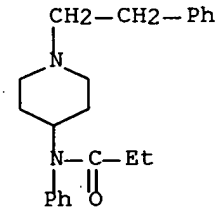
CC 1-11 (Pharmacology)

IT ***437-38-7***, Fentanyl 7440-63-3, Xenon, biological studies 59467-70-8, Midazolam
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalational administration of xenon improved recovery from myocardial stunning and had improved wall-thickening and attenuated increase in plasma epinephrine in chronically instrumented dog under fentanyl/midazolam anesthesia)

IT ***437-38-7***, Fentanyl
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalational administration of xenon improved recovery from myocardial stunning and had improved wall-thickening and attenuated increase in plasma epinephrine in chronically instrumented dog under fentanyl/midazolam anesthesia)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 29 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:526511 HCAPLUS Full-text

DOCUMENT NUMBER: 141:66401

TITLE: LC-MS-MS screening of piritramide and other opiates in hair

AUTHOR(S): Sachs, Hans; Thieme, Detlef; Anielski, Patricia

CORPORATE SOURCE: Institut fuer Rechtsmedizin, Universitaet Muenchen, Munich, D-80337, Germany

SOURCE: GTFCh-Symposium: Ausgewaehlte Aspekte der Forensischen Toxikologie, Beitraege zum Symposium der Gesellschaft fuer Toxikologische und Forensische Chemie, 13th, Mosbach, Germany, Apr. 3-5, 2003 (2004), Meeting Date 2003, 392-396. Editor(s): Pragst, Fritz; Aderjan, Rolf. Verlag Dr. Dieter Helm: Heppenheim, Germany. CODEN: 69FPB6; ISBN: 3-923032-16-1

DOCUMENT TYPE: Conference

LANGUAGE: German

AB When ampoules of opioids are stolen from intensive care stations the members of the clin. staff are the 1st suspected subjects. In those cases it is often tried to control the staff by hair anal. examining the sample on the special drug. It is known that morphine is part of a general hair screening. But for other opioids like meperidine, buprenorphine, or pentazocine special methods

are needed and piritramide has, to our knowledge, never been detected in hair samples. Using LC-MS-MS technique it was able to build up a screening procedure in which common opiates (morphine, dihydrocodeine, codeine, acetylmorphine) as well as other opioids (pentazocine, meperidine, piritramide, fentanyl, sufentanil) are detected. An XDB C8 (Zorbax, 4.6 mm + 75 mm + 3.5 μm) column, protected by an XDB C18 (Zorbax) 4 mm + 4 mm + 5 μm guard column was applied for chromatog. ***separation*** The binary mobile phase gradient [10% B (0 - 1 min) → 10 to 90% B (1 - 9 min) → 90% B, (9 - 10 min)] was formed by solvent A (0.2 mM ammonium acetate (NH4ac) in water + acetonitrile (95+5)) and solvent B (0.2 mM NH4ac in water + acetonitrile (5+95)) at a constant flow of 0.7 mL/min. The most important results were the findings of piritramide in the methanol extracted hair of a nurse and a female nurse. While the male subject showed a concentration of 0.637 ng/mg in a hair of 3.5 cm of length. From the hair of the nurse 0.003 to 0.004 ng/mg of piritramide could be extracted The second important result was that the buffer extraction is less efficient concerning piritramide. From the hair of the male nurse only 0.032 ng/mg could be extracted with Soerensen buffer (pH 7.4). The equally extracted hair of the female was neg.

CC 4-2 (Toxicology)

IT Mass spectrometry
(***liquid chromatog.*** combined with; piritramide and opiates in hair determined by LC-MS-MS)

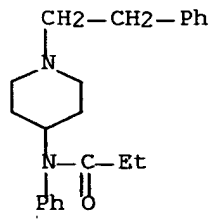
IT ***Liquid chromatography***
(mass spectrometry combined with; piritramide and opiates in hair determined by LC-MS-MS)

IT 57-27-2, Morphine, analysis 57-42-1, Pethidine 76-57-3, Codeine 76-99-3, Methadone 125-28-0, Dihydrocodeine 127-35-5, Phenazocine 302-41-0, Piritramide 359-83-1, Pentazocine ***437-38-7***, Fentanyl 469-62-5, Propoxyphene 1893-33-0, Pipamperone 2784-73-8, 6-Acetylmorphine 30223-73-5, EDDP 38677-94-0, Nor-tilidine 51931-66-9, Tilidine 52485-79-7, Buprenorphine
RL: ANT (Analyte); POL (Pollutant); ANST (Analytical study); OCCU (Occurrence)
(piritramide and opiates in hair determined by LC-MS-MS)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); POL (Pollutant); ANST (Analytical study); OCCU (Occurrence)
(piritramide and opiates in hair determined by LC-MS-MS)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 30 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:975711 HCAPLUS Full-text
DOCUMENT NUMBER: 142:487712

TITLE: Quality evaluation and standardization of fentanyl and the related injection preparation

AUTHOR(S): Murashova, U. A.; Sadchikova, N. P.; Skalkina, L. V.; Smirnov, S. K.

CORPORATE SOURCE: State Institute of Organic Chemistry and Technology, Federal Scientific Center, Moscow, Russia

SOURCE: Pharmaceutical Chemistry Journal (Translation of Khimiko-Farmatsevticheskii Zhurnal) (2004), 38(6), 336-338
CODEN: PCJOAU; ISSN: 0091-150X

PUBLISHER: Springer Science+Business Media, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB ***HPLC*** procedures were developed for the quality control of fentanyl in injection solns. with respect to the content of foreign impurities and quant. determination of the parent substance. The proposed method was successfully used for evaluation of the quality of a com. preparation and for optimization of the conditions of ***purification*** of the parent substance. The methods and characteristics are included into the pharmacopeial articles of manufacturer for fentanyl and 0.005% fentanyl solution for injections.

CC 64-3 (Pharmaceutical Analysis)

ST fentanyl injection quality control ***HPLC; liq chromatog*** fentanyl detn injection

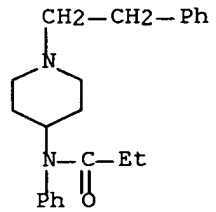
IT ***HPLC***
Quality control
(quality evaluation and determination of fentanyl in injection solns.)

IT ***437-38-7,*** Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(quality evaluation and determination of fentanyl in injection solns.)

IT ***437-38-7,*** Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(quality evaluation and determination of fentanyl in injection solns.)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 31 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:526500 HCAPLUS Full-text

DOCUMENT NUMBER: 141:290209

TITLE: Simple APCI-LC-MS method for screening, library-assisted identification and validated quantification of anesthetics, benzodiazepines and low dosed opioids in plasma often asked for in the context of the diagnosis of brain death

AUTHOR(S): Kratzsch, Carsten; Peters, Frank T.; Kraemer, Thomas; Weber, Armin A.; Maurer, Hans H.
CORPORATE SOURCE: Department of Experimental and Clinical Toxicology. Institut of Experimental and Clinical Pharmacology and Toxicology, University of Saarland, Homburg, D-66421, Germany
SOURCE: GTFCh-Symposium: Ausgewaehlte Aspekte der Forensischen Toxikologie, Beitraege zum Symposium der Gesellschaft fuer Toxikologische und Forensische Chemie, 13th, Mosbach, Germany, Apr. 3-5, 2003 (2004), Meeting Date 2003, 299-309. Editor(s): Pragst, Fritz; Aderjan, Rolf. Verlag Dr. Dieter Helm: Heppenheim, Germany. CODEN: 69FPB6; ISBN: 3-923032-16-1
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The determination of various drugs from different drug classes acting on the central nervous system is a prerequisite in the process of the diagnosis of brain death. Therefore an atmospheric pressure chemical ionization ***liq . chromatog.***-mass spectrometric assay (APCI-LC-MS) was developed for screening, identification and quantification of etomidate, ketamine, clonazepam, diazepam, flunitrazepam (including its two metabolites 7-aminoflunitrazepam and norflunitrazepam), midazolam, nordazepam, alfentanil, fentanyl, sufentanil and piritramide in plasma. After liquid-liquid extraction, the analytes and the five deuterated internal stds. (diazepam-d5, fentanyl-d5, flunitrazepam-d7, ketamine-d4 and nordazepam-d5) were ***separated*** using fast gradient elution. After screening and identification in the scan mode using the authors' new LC-MS library, the analytes were quantified in the selected-ion mode. The quantification assay was fully validated according to internationally accepted criteria. It was found to be selective and proved to be linear from sub therapeutic to over therapeutic concns. for all analytes. The accuracy and precision data were within the required limits. The validated LC-MS assay was successfully applied to authentic cases in the diagnosis of brain death.

CC 4-2 (Toxicology)
Section cross-reference(s): 1

IT Mass spectrometry
(***liquid chromatog.*** combined with; simple APCI-LC-MS method for screening, library-assisted identification and validated quantification of anesthetics, benzodiazepines and low dosed opioids in plasma often asked for in the context of the diagnosis of brain death)

IT ***Liquid chromatography***
(mass spectrometry combined with; simple APCI-LC-MS method for screening, library-assisted identification and validated quantification of anesthetics, benzodiazepines and low dosed opioids in plasma often asked for in the context of the diagnosis of brain death)

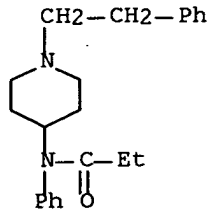
IT 302-41-0, Piritramide ***437-38-7,*** Fentanyl 439-14-5, Diazepam 1088-11-5, Nordazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 2558-30-7, Norflunitrazepam 6740-88-1, Ketamine 12794-10-4D, Benzodiazepine, derivs. 33125-97-2, Etomidate 34084-50-9, 7-Aminoflunitrazepam 56030-54-7, Sufentanil 59467-70-8, Midazolam 71195-58-9, Alfentanil
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); PAC (Pharmacological activity); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(simple APCI-LC-MS method for screening, library-assisted identification and validated quantification of anesthetics, benzodiazepines and low dosed opioids in plasma often asked for in the context of the diagnosis of brain death)

IT ***437-38-7,*** Fentanyl
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); PAC (Pharmacological activity); THU (Therapeutic use); ANST (Analytical

study); BIOL (Biological study); USES (Uses)
(simple APCI-LC-MS method for screening, library-assisted identification and validated quantification of anesthetics, benzodiazepines and low dosed opioids in plasma often asked for in the context of the diagnosis of brain death)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 32 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:236185 HCAPLUS Full-text
DOCUMENT NUMBER: 139:316623
TITLE: Simultaneous assessment of drug interactions with low- and high-extraction opioids: Application to parecoxib effects on the pharmacokinetics and pharmacodynamics of fentanyl and alfentanil
AUTHOR(S): Ibrahim, Andra E.; Feldman, Jennifer; Karim, Aziz; Kharasch, Evan D.
CORPORATE SOURCE: Dep. Anesthesiology, University of Washington., USA
SOURCE: Anesthesiology (2003), 98(4), 853-861
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Parecoxib is a parenteral cyclooxygenase-2 (COX-2) inhibitor intended for perioperative analgesia. It is an inactive prodrug hydrolyzed in vivo to the active inhibitor valdecoxib, a substrate for hepatic cytochrome P 450 3A4 (CYP3A4); hence, a potential exists for metabolic interactions with other CYP3A substrates. This study determined the effects of parecoxib on the pharmacokinetics and pharmacodynamics of the CYP3A substrates fentanyl and alfentanil compared with the CYP3A inhibitor troleandomycin. Alfentanil is a low-extraction drug with a clearance that is highly susceptible to drug interactions; fentanyl is a high-extraction drug and, thus, is theor. less vulnerable. The authors therefore also tested the hypothesis that the extraction ratio influences the consequence of altered hepatic metabolism of these opioids. After Institutional Review Board-approved, written, informed consent was obtained, 12 22- to 40-yr-old healthy volunteers were enrolled in the study. The protocol was a randomized, double-blinded, balanced, placebo-controlled, 3-session (placebo, parecoxib, or troleandomycin pretreatment) crossover. Subjects received both alfentanil (15 μg/kg) and fentanyl (5 μg/kg; 15-min i.v. infusion) 1 h after placebo, parecoxib (40 mg i.v. every 12 h), or troleandomycin (every 6 h). Study sessions were ***separated*** by 7 or more days. Opioid concns. in venous blood were determined by ***liquid chromatog.***-mass spectrometry. Pharmacokinetic parameters were determined by

noncompartmental anal. Opioid effects were determined by pupillometry, respiratory rate, and Visual Analog Scale scores. There were no significant differences between the placebo and parecoxib treatments in alfentanil or fentanyl plasma concentration, maximum observed plasma concentration, area under the plasma time-concentration time curve, clearance, elimination half-life, or volume of distribution. However, disposition of alfentanil, and to a lesser extent fentanyl, was significantly altered by troleandomycin. Clearances were reduced to 12% (0.64 mL · kg-1 · min-1) and 61% (9.35) of control (5.53 and 15.3) for alfentanil and fentanyl. Pupil diameter vs. time curves were similar between placebo and parecoxib treatments but were significantly different after troleandomycin. Single-dose parecoxib does not alter fentanyl or alfentanil disposition or clin. effects and does not appear to cause significant CYP3A drug interactions. CYP3A inhibition decreases alfentanil clearance more than fentanyl clearance, confirming that the extraction ratio influences the consequence of altered hepatic drug metabolism Modified cassette, or "cocktail" dosing is useful for assessing drug interactions in humans.

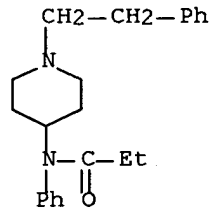
CC 1-4 (Pharmacology)

IT ***437-38-7***, Fentanyl 71195-58-9, Alfentanil 198470-84-7, Parecoxib
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(parecoxib effects on pharmacokinetics and pharmacodynamics of fentanyl and alfentanil)

IT ***437-38-7***, Fentanyl
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(parecoxib effects on pharmacokinetics and pharmacodynamics of fentanyl and alfentanil)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 33 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:911165 HCAPLUS Full-text
DOCUMENT NUMBER: 140:82394
TITLE: Simultaneous determination of fentanyl citrate, ketamine hydrochloride, and droperidol in 0.9% sodium chloride by ***HPLC***
AUTHOR(S): Lee, Derek K. T.; Harsono, Rusly; Wong, Chi-Yin; Wang, Da-Peng
CORPORATE SOURCE: Department of Pharmacy, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
SOURCE: Chinese Pharmaceutical Journal (Taipei, Taiwan)

(2003), 55(2), 147-152
CODEN: CPHJEP; ISSN: 1016-1015
PUBLISHER: Pharmaceutical Society of Republic of China
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A simple and rapid ***liquid chromatog.*** method is presented for the determination of fentanyl citrate, ketamine hydrochloride, and droperidol in 0.9% NaCl injection stored in polyvinyl chloride (PVC) infusion bags. The assay was performed on a pre-packed ***HPLC*** Hypersil BDS Ph 4.6 mm + 15 cm, 3 μm column under controlled ambient temperature Peak ***separation*** among fentanyl citrate, ketamine hydrochloride, droperidol, and their associated degradation compds. was achieved by isocratic elution with a mobile phase consisting of 50% (volume/volume) MeOH and 50% 0.0015 M tetra-Bu ammonium hydroxide in 0.2 M phosphate buffer (pH 4.8) at a flow rate of 1.3 mL/min A UV/VIS variable programmable wavelength detector set at 230 nm. was used. Sample vols. of 20 μL were injected. There was no need for sample pre-treatment.

CC 64-3 (Pharmaceutical Analysis)

ST fentanyl citrate ketamine hydrochloride droperidol ***HPLC***

IT ***HPLC***
Resolution (***separation***)
(simultaneous determination of fentanyl citrate, ketamine hydrochloride and droperidol in 0.9% NaCl by ***HPLC***)

IT 548-73-2, Droperidol ***990-73-8***, Fentanyl citrate 1867-66-9, Ketamine hydrochloride
RL: ANT (Analyte); ANST (Analytical study)
(simultaneous determination of fentanyl citrate, ketamine hydrochloride and droperidol in 0.9% NaCl by ***HPLC***)

IT ***990-73-8***, Fentanyl citrate
RL: ANT (Analyte); ANST (Analytical study)
(simultaneous determination of fentanyl citrate, ketamine hydrochloride and droperidol in 0.9% NaCl by ***HPLC***)

RN 990-73-8 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (CA INDEX NAME)

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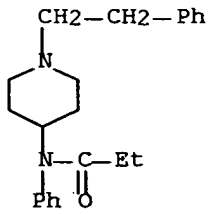
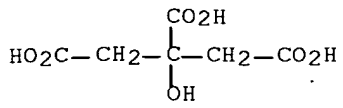
CRN 437-38-7
CMF C22 H28 N2 O



CM 2

CRN 77-92-9
CMF C6 H8 O7



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 34 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:537072 HCAPLUS Full-text
DOCUMENT NUMBER: 138:32746
TITLE: Chromatographic approach for determining the relative membrane permeability of drugs
AUTHOR(S): Meng, Qing C.; Johansson, Jonas S.; Eckenhoff, Roderic G.
CORPORATE SOURCE: Center for Research in Anesthesia, Department of Anesthesia, University of Pennsylvania Health System, Philadelphia, PA, 19104, USA
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2002), 774(1), 89-95
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB By determining the exptl. dependence of the theor. plate height (H) on the flow rate (U), values of diffusion coeffs. such as the permeation rate of compds. in a polymeric stationary phase were calculated by measuring solute mass transfer. This approach is proposed for modeling the relative diffusion rate of a drug within a membrane. After the ***separation*** of opioid compds. by using a C18-derivatized polystyrene-divinylbenzene polymer ***HPLC*** column, the slopes of H-U plots increased quant. in the order meperidine < alfentanil < fentanyl < sufentanil, indicating that the large mass transfer resistance slows the penetration of mols. A constant intercept for the exptl. plate height supported the proposal interpretation. A good correlation between the diffusion coeffs. and the hydrophobicity (log Poctanol), determined by the traditional shake-flask method, was obtained for the opioid compds., demonstrating that the more lipophilic mols. penetrate deeper into the stationary phase, leading to a lower migration rate under these conditions. A plot of the diffusion coeffs. vs. the previously reported potency ratios for the opioids after i.v. administration reflected the value of such a dynamic process in drug studies. The present work differed from previous studies by measuring the permeability of drugs in the stationary phase rather than providing membrane partition coeffs. for a series of analogs. Thus, the study of drug permeability, combined with other physicochem. properties, such as hydrophobicity, may provide addnl. information on drug-membrane interactions.

CC 1-1 (Pharmacology)
Section cross-reference(s): 63

ST opioid permeability biol membrane diffusion coeff hydrophobicity; ***HPLC*** model drug diffusion cell membrane diffusion coeff hydrophobicity

IT Cell membrane
Drugs
HPLC
Membrane, biological
Permeability
Simulation and Modeling

(***HPLC*** model for determining the relative membrane permeability of drugs)

IT Diffusion
(***HPLC*** model for determining the relative membrane permeability of drugs by measuring)

IT Hydrophobicity
Lipophilicity
(***HPLC*** model for determining the relative membrane permeability of drugs in relation to)

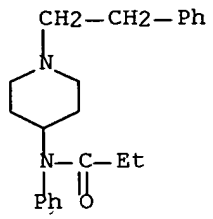
IT Opioids
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(***HPLC*** model for determining the relative membrane permeability of drugs such as)

IT 57-42-1, Meperidine ***437-38-7***, Fentanyl 56030-54-7, Sufentanil 71195-58-9, Alfentanil
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(***HPLC*** model for determining the relative membrane permeability of drugs such as)

IT ***437-38-7***, Fentanyl
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(***HPLC*** model for determining the relative membrane permeability of drugs such as)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 35 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:505671 HCAPLUS Full-text

DOCUMENT NUMBER: 137:74566

TITLE: Simultaneous determination of in total 17 opium alkaloids and opioids in blood and urine by fast ***liquid chromatography***-diode-array detection-fluorescence detection, after solid-phase extraction

AUTHOR(S): Dams, R.; Benijts, T.; Lambert, W. E.; De Leenheer, A. P.

CORPORATE SOURCE: Laboratorium voor Toxicologie, Universiteit Gent, Ghent, B-9000, Belg.

SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2002), 773(1), 53-61

CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A fast ***liquid chromatog.*** method with tandem diode array-fluorescence detection for the simultaneous determination of in total 17 opium alkaloids and opioids is presented. Blank blood and urine samples (1 mL) were spiked with different concns. of a standard mixture, as well as with the internal standard, butorphanol (2000 ng/mL). After solid-phase extraction, based on weak cation exchange (Bond Elut CBA SPE columns), the exts. were examined by ***HPLC***-DAD-FL. By using a "high-speed" Ph column (53+7.0 mm I.D., particle size 3 μm) eluted with a gradient system (A: water-methanol (90:10, volume/volume), B: methanol, both containing 25 mM triethylammoniumformate (pHA =4.5)) all compds. could be baseline ***separated*** within 12 min. The method was validated and its applicability was demonstrated by the anal. of real-time forensic cases.

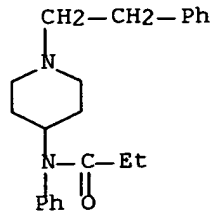
CC 4-2 (Toxicology)

IT 50-03-3, Cortisol acetate 50-06-6, Phenobarbital, analysis 50-36-2, Cocaine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-53-3, Chlorpromazine, analysis 50-81-7, Ascorbic acid, analysis 52-86-8, Haloperidol 53-86-1, Indomethacine 54-11-5, Nicotine 55-38-9, Fenthion 56-29-1, Hexobarbital 57-24-9, Strychnine 57-41-0, Phenytoine 57-42-1, Pethidine 58-08-2, Caffeine, analysis 58-25-3, Chlordiazepoxide 58-32-2, Dipyridamole 58-55-9, Theophylline, analysis 58-73-1, Diphenhydramine 59-46-1, Procaine 62-44-2, Phenacetine 69-72-7, Salicylic acid, analysis 72-44-6, Methaqualone 76-42-6, Oxycodone 76-73-3, Secobarbital 77-36-1, Chlorthalidone 83-67-0, Theobromine 97-77-8, Disulfiram 103-90-2, Acetaminophen 113-15-5, Ergotamine 113-53-1, Dosulepine 130-95-0, Quinine 137-58-6, Lidocaine 298-46-4, Carbamazepine 357-56-2, Dextromoramide 364-62-5, Metoclopramide ***437-38-7***, Fentanyl 458-24-2, Fenfluramine 509-67-1, Pholcodine 519-09-5, Benzoylecgonine 564-25-0, Doxycycline 603-50-9, Bisacodyl 739-71-9, Trimipramine 846-49-1, Lorazepam 848-75-9, Lormetazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1668-19-5, Doxepine 1812-30-2, Bromazepam 2898-12-6, Medazepam 4764-17-4, MDA 5118-29-6, Melitracen 5638-76-6, β-Histine 15687-27-1, Ibuprofen 17617-23-1, Flurazepam 19794-93-5, Trazodone 22316-47-8, Clobazam 24166-13-0, Cloxazolam 24937-78-8, EVA 26787-78-0, Amoxicillin 27203-92-5, Tramadol 36104-80-0, Camazepam 42399-41-7, Diltiazem 42542-10-9, XTC 43200-80-2, Zopiclone 51931-66-9, Tilidine 54143-55-4, Flecainide 54910-89-3, Fluoxetine 57801-81-7, Brotizolam 57808-66-9, Domperidone 59467-70-8, Midazolam 59729-33-8, Citalopram 59804-37-4, Tenoxicam 61869-08-7, Paroxetine
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(opium alkaloids and opioids simultaneous determined in blood and urine by fast LC with tandem diode array-fluorescence detection and interference)

IT ***437-38-7***, Fentanyl
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(opium alkaloids and opioids simultaneous determined in blood and urine by fast LC with tandem diode array-fluorescence detection and interference)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 36 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:167364 HCAPLUS Full-text
DOCUMENT NUMBER: 130:346780
TITLE: Simultaneous determination of fentanyl and midazolam using high-performance ***liquid chromatography*** with ultraviolet detection
AUTHOR(S): Portier, E. J. G.; de Blok, K.; Butter, J. J.; van Boxtel, C. J.
CORPORATE SOURCE: Department of Clinical Pharmacology and Pharmacotherapy, Academic Medical Center, Amsterdam, 1105 A2, Neth.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 723(1 + 2), 313-318
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

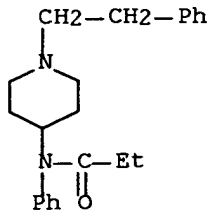
AB When measuring fentanyl and midazolam simultaneously in the same plasma sample with standard high-performance ***liquid chromatog.***-UV (***HPLC***-UV) detection, overlap of the fentanyl peak by the midazolam peak occurs, which makes fentanyl determination impossible. We tested the hypothesis that by acidifying the methanol mobile phase with 0.02% perchloric acid, 70%, it would be possible to ***sep.*** both peaks. The UV detector was set at 200 nm. Calibration curves for fentanyl (range 0-2000 pg/mL) and midazolam (range 0-400 ng/mL) were linear (r>0.99). The detection limits were 200 pg/mL (fentanyl) and 10 ng/mL (midazolam). Precision and accuracy for intra- and inter-assay variability as well as in-line validation with quality control samples (QCS) were acceptable (< 15 and 20%, resp.), except for fentanyl QCS of 200 pg/mL (17.8% precision). Although less sensitive than gas chromatog.-mass spectrometry (GC-MS), reliable measurements of fentanyl, simultaneously with midazolam, can be performed with this ***HPLC***-UV system.

CC 1-1 (Pharmacology)
ST fentanyl midazolam detn blood ***liq chromatog;*** ***HPLC*** fentanyl midazolam detn
IT Blood analysis
(simultaneous determination of fentanyl and midazolam using high-performance ***liquid chromatog.*** with UV detection)
IT ***437-38-7***, Fentanyl 59467-70-8, Midazolam
RL: ANT (Analyte); ANST (Analytical study)
(simultaneous determination of fentanyl and midazolam using high-performance ***liquid chromatog.*** with UV detection)
IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)

(simultaneous determination of fentanyl and midazolam using high-performance
liquid chromatog. with UV detection)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 37 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:319922 HCAPLUS Full-text

DOCUMENT NUMBER: 126:338739

TITLE: Sex differences in discriminative stimulus effects of morphine in the rat

AUTHOR(S): Craft, R. M.; Kalivas, P. W.; Stratmann, J. A.

CORPORATE SOURCE: Department of Psychology, Washington State University, Pullman, WA, 99164-6520, USA

SOURCE: Behavioural Pharmacology (1996), 7(8), 764-778
CODEN: BPHAEL; ISSN: 0955-8810

PUBLISHER: Rapid Science Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Female and male rats were trained to discriminate 3.0 mg morphine/kg, s.c., from saline. The female rats that acquired and maintained the morphine discrimination did so in fewer sessions than the males did, and the ED50 for morphine substitution was lower in females. The time course of morphine substitution was approx. equivalent in females and males. The μ-agonist fentanyl completely substituted for morphine in both sexes, with no sex difference in potency to substitute for morphine. The μ-agonist buprenorphine partially or completely substituted for morphine in all the females and in five of 6 males, but at a lower dose in females. The δ-agonist BW373U86 partially substituted for morphine in both sexes, with no potency differences; the κ-agonist U69,593 and the nonopioid cocaine did not substitute for morphine in either sex. On a test of spontaneous locomotor activity, morphine increased locomotion to a slightly but not significantly greater extent in males than in females. Morphine also produced greater hotplate antinociception in males than in females. Further drug-discrimination training with a lower dose of morphine (1.0 mg/kg) decreased the ED50 for morphine substitution in females and males to the same extent. In a ***sep.*** group of age-matched rats, there was no sex difference in brain or plasma levels of morphine measured by ***HPLC*** 20 min postinjection, the same time interval used to examine the behavioral effects of morphine. The ***HPLC*** results, plus the fact that sex differences were not the same for all behavioral effects of morphine, suggest that the sex differences in the discriminative stimulus effects of morphine are not due to differential pharmacokinetics. The possibility that the sex differences in morphine

discrimination reflect sex differences in opioid receptor pharmacol., or differential reinforcement between the morphine and saline levers for males but not females, is discussed.

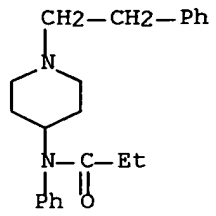
CC 1-11 (Pharmacology)

IT 50-36-2, Cocaine ***437-38-7***, Fentanyl 52485-79-7, Buprenorphine 96744-75-1 155836-52-5, BW 373U86
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sex differences in the discriminative stimulus effects of morphine response to)

IT ***437-38-7***, Fentanyl
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sex differences in the discriminative stimulus effects of morphine response to)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L112 ANSWER 38 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:407564 HCAPLUS Full-text
DOCUMENT NUMBER: 125:131504
TITLE: A sensitive assay for the simultaneous measurement of alfentanil and fentanyl in plasma
AUTHOR(S): Kumar, K.; Ballantyne, J. A.; Baker, A. B.
CORPORATE SOURCE: Sch. Pharm., Univ. Otago, Dunedin, N. Z.
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (1996), 14(6), 667-673
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A reversed-phase high-performance ***liquid chromatog.*** method for the simultaneous determination of plasma concns. of the narcotic analgesics alfentanil and fentanyl using papaverine hydrochloride as the internal standard is presented. Chromatog. ***seps.*** were achieved with an Econosphere CN, 5 μm, 25 cm x 4.6 mm i.d. column and the effluent was monitored at 195 nm. The assay was linear over the clin. relevant plasma range of 2-2000 ng ml-1 for alfentanil and 2-100 ng ml-1 for fentanyl and has the sensitivity and specificity necessary to determine plasma concns. of these compds. Inter- and intra-day precision (RSD) for both compds. did not exceed 10% in these ranges. The assay procedure was utilized for pharmacokinetic studies of plasma concns. in subjects receiving alfentanil and fentanyl during and after cardiac

surgery. This will allow better elucidation of pharmacokinetic variables in this populace.

CC 1-1 (Pharmacology)

ST alfentanil fentanyl detn plasma ***HPLC; liq chromatog*** alfentanil fentanyl plasma

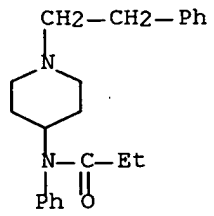
IT Blood analysis
Pharmacokinetics
(alfentanil and fentanyl simultaneous determination in human blood plasma by
reversed-phase ***HPLC***)

IT ***437-38-7***, Fentanyl 71195-58-9, Alfentanil
RL: ANT (Analyte); ANST (Analytical study)
(alfentanil and fentanyl simultaneous determination in human blood plasma by
reversed-phase ***HPLC***)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(alfentanil and fentanyl simultaneous determination in human blood plasma by
reversed-phase ***HPLC***)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 39 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:115851 HCAPLUS Full-text

DOCUMENT NUMBER: 126:182367

TITLE: Rapid clinical forensic toxicological analysis using full automatic high performance ***liquid chromatography*** system

AUTHOR(S): Ohtsuji, Masahiko

CORPORATE SOURCE: Department of Legal Medicine, School of Medicine, Kanazawa University, Kanazawa, 920, Japan

SOURCE: Kanazawa Daigaku Juzen Igakkai Zasshi (1996), 105(5), 627-647
CODEN: JUZIAG; ISSN: 0022-7226

PUBLISHER: Juzen Igakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Toxicol. anal. on human specimens such as body fluid is very important in clin. and forensic medicine. Many anal. instruments have already been developed, and they are now available in the medical field. In practice, those instruments are, however, used for definite confirmation of a drug or poison that is already known or strongly suspected to have existed in the specimen tested. It is, however, much more important and necessary to rapidly and systematically explore drugs or poisons in emergency medical cases and

forensic autopsy cases with no or little toxicol. information. In this study, the full automatic high performance ***liquid chromatog.*** system, REMEDi-HS system was used, and its possibility for drug identification in those specimens with no toxicol. information was systematically examined Forty-two kinds of widely used drugs and their metabolites, being selected from among such drug groups as antipsychotics, hypnotics, antihistaminics, local anesthetics, etc., were exptl. added to distilled water, serum and urine, and it was examined whether this instrument could correctly identify these substances or not. The result was that 38 compds. (but not four acidic drugs) were correctly identified by REMEDi-HS. Eight local anesthetics and two lidocaine metabolites could be simultaneously ***separated*** as different peaks in a specimen and correctly identified as well by this system. The qual. anal. of these compds. in specimens was not influenced by the hydrogen ion concentration ranging from pH 4 to pH 9. Methamphetamine, its metabolites, amphetamine, ephedrine and methylephedrine could be also correctly identified even in putrefied specimens. Calibration curves for 24 kinds of drugs and metabolites were prepared by plotting the peak height ratio of each standard to chlorpheniramine, internal standard, against the concentration to examine the possibility of quant. anal. by the REMEDi-HS system, and they showed excellent linearity. Detection limits of these compds. were about 0.1 μg/mL. The sensitivity of this system for these compds. was better than that of the thin-layer chromatog. system usually used in Japan. Therapeutic drug monitoring for prilocaine, lidocaine, mepivacaine, bupivacaine and carbamazepine was considered fully feasible because their detection limits by REMEDi-HS were much lower than their therapeutic blood levels. Quant. values of bromisovalum, ephedrine, hydroxyzine, diphenhydramine, ranitidine, lidocaine and glycinexylidide in serum, urine and gastric matrixes using quantitation factors, being determined for approx. 450 different kinds of drugs and metabolites by the manufacturer based on the average ratio of drug concentration against the peak height, were compared with the results by multi-point calibration method. Then each regression line between the values given by these two different methods gave good correlation coefficient, ranging from 0.960 to 1.000. When the values of lidocaine, monoethylglycinexylidide and bromisovalum in serum and urine measured by multi-point calibration method were compared with those by gas chromatog.-mass spectrometry methods, thus showing good correlations (0.753 to 0.978). Within-run and day-to-day precision coeffs. of variation, being examined with eight local anesthetics and two lidocaine metabolites, were from 1.07 to 8.35%, and 1.91 to 11.8%, resp. The hydrogen ion concentration had no influence on the quant. anal. of these ten compds. The serum and urine, obtained from human volunteers and a rabbit to whom an over the counter drug or lidocaine was administered, resp., were analyzed, and then the administered drugs and their metabolites were correctly detected. Out of 79 autopsies and 53 clin. cases, of which specimens were analyzed by REMEDi-HS every drug or metabolite was detected in 61 autopsies and 46 clin. cases. Drug identification by REMEDi-HS was shown to be very useful for diagnosis and/or therapy in these autopsy and clin. cases. Drug monitoring of lidocaine and its metabolite, MEGX, was performed in three cases of acute myocardial infarction with i.v. lidocaine administration, and REMEDi-HS was also shown to be useful in drug effect certification and side effect prevention. From these results obtained, it has been well demonstrated that REMEDi-HS contributes significantly to rapid and comprehensive drug anal. in both forensic toxicol. practice and emergency medicine.

CC 4-2 (Toxicology)
Section cross-reference(s): 1, 9

ST clin forensic toxicity analysis ***HPLC; liq chromatog*** clin forensic toxicol analysis

IT Aging, animal
Blood analysis
Forensic analysis

Forensic chemistry
HPLC
Pharmacokinetics
Sex
TLC (thin layer chromatography)
Toxicity
Urine analysis
(clin. forensic toxicol. anal. using full automatic high performance ***liquid chromatog.*** system)

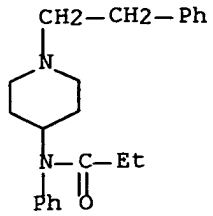
IT Forensic analysis
Forensic analysis
(drug; clin. forensic toxicol. anal. using full automatic high performance ***liquid chromatog.*** system)

IT Heart, disease
(infarction; clin. forensic toxicol. anal. using full automatic high performance ***liquid chromatog.*** system)

IT 50-06-6, Phenobarbital, analysis 50-18-0, Cyclophosphamide 50-23-7, Hydrocortisone 50-48-6, Amitriptyline 50-53-3D, Chlorpromazine, metabolites 52-53-9D, Verapamil, metabolites 56-29-1, Hexobarbital 56-54-2, Quinidine 57-41-0, Phenytoin 58-08-2, Caffeine, analysis 58-39-9, Perphenazine 58-73-1, Diphenhydramine 58-73-1D, Diphenhydramine, metabolites 60-87-7, Promethazine 60-87-7D, Promethazine, metabolites 64-04-0, Phenethylamine 68-88-2, Hydroxyzine 76-99-3, Methadone 77-10-1, Phencyclidine 77-17-8, Desmethylmeperidine 77-65-6, Carbromal 83-43-2, Methylprednisolone 84-06-0, Thiopropazate 113-45-1, Methylphenidate 113-53-1, Dothiepin 113-92-8 113-92-8D, metabolites 114-07-8, Erythromycin 115-46-8, Azacyclonol 125-28-0, Dihydrocodeine 125-28-0D, Dihydrocodeine, metabolites 125-84-8, Aminoglutethimide 137-58-6, Lidocaine 298-46-4, Carbamazepine 298-46-4D, Carbamazepine, metabolites 299-42-3, Ephedrine 364-62-5, Metoclopramide ***437-38-7***, Fentanyl 439-14-5, Diazepam 496-67-3, Bromisovalum 528-92-7, Apronalide 537-46-2, Methamphetamine 552-79-4, Methylephedrine 835-31-4, Naphazoline 1491-59-4, Oxymetazoline 6740-88-1, Ketamine 7640-51-9, Promethazine sulfoxide 7728-40-7, Monoethylglycinexylidide 10262-69-8, Maprotiline 13523-86-9, Pindolol 15676-16-1, Sulpiride 15686-51-8, Clemastine 17471-10-2, N-Desmethyldiphenhydramine 18865-38-8, Glycinexylidide 19794-93-5, Trazodone 27220-47-9, Econazole 29975-16-4, Estazolam 35941-65-2, Butriptyline 36507-30-9, Carbamazepine-10,11-epoxide 38396-39-3, Bupivacaine 42399-41-7D, Diltiazem, metabolites 51481-61-9, Cimetidine 52365-63-6, Dipivefrine 59878-63-6, Desmethylzopiclone 63659-18-7, Betaxolol 66357-35-5, Ranitidine 66357-35-5D, Ranitidine, metabolites 67018-85-3 79617-96-2D, Sertraline, metabolites
RL: ANT (Analyte); ANST (Analytical study)
(clin. forensic toxicol. anal. using full automatic high performance ***liquid chromatog.*** system)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(clin. forensic toxicol. anal. using full automatic high performance ***liquid chromatog.*** system)

RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)

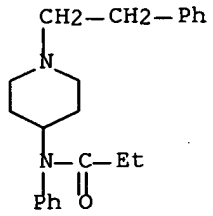


L112 ANSWER 40 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:732599 HCAPLUS Full-text
DOCUMENT NUMBER: 123:132730
TITLE: Pharmacokinetics of propofol infusion in Asian patients undergoing coronary artery bypass grafting
AUTHOR(S): Lee, How-Sung; Khoo, Yok-Moi; Chua, Bee-Choo; Ng, Agnes Suah-Bee; Tan, Shani Sian-Wei; Chew, Sook-Leung
CORPORATE SOURCE: Dep. of Pharmacology, National Univ. of Singapore, Singapore
SOURCE: Therapeutic Drug Monitoring (1995), 17(4), 336-41
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacokinetics of propofol was studied in 11 Asian patients with fentanyl-isoflurane anesthesia during cardiopulmonary bypass (CPB) and undergoing elective coronary artery bypass grafting (CABG). Instead of the usual increments of morphine and a benzodiazepine, propofol (4 mg/kg/h) was initiated at the start of CPB and ceased at CPBB ***sepn*** . Whole blood propofol concns. were determined during and postinfusion using high-performance ***liquid chromatog.*** with fluorescence detection. Data from four patients seemed to fit a two-compartment model, whereas those from seven patients were significantly (F test, $p < 0.05$) better fitted to a three-compartment model. The pharmacokinetic parameters were as follows: the mean (SD) of the initial distribution phase $t1/2\pi$, intermediate distribution phase $t1/2\alpha$, and elimination phase $t1/2\beta$ were 2.22 (1.04) min, 42.9 (16.4) min, and 370 (138) min, resp. The mean clearance of 1.31 (0.50) L/min was lower than those reported from other studies, whereas the mean blood concentration of 2.2 (1.0) mg/L at the 1-h infusion period was higher. The mean calculated apparent C ss was 3.9 (1.5) mg/L. The low clearance is likely to be due to hemodynamic changes during CPB and CABG, thereby affecting drug distribution and blood flow to the liver.

CC 1-11 (Pharmacology)
IT ***437-38-7***, Fentanyl 26675-46-7, Isoflurane
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of propofol infusion in patients undergoing coronary artery bypass grafting)
IT ***437-38-7***, Fentanyl
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of propofol infusion in patients undergoing coronary artery bypass grafting)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX

NAME)



L112 ANSWER 41 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:436460 HCAPLUS Full-text
DOCUMENT NUMBER: 122:180434
TITLE: Identification power of a standardized ***HPLC*** -DAD system for systematic toxicological analysis
AUTHOR(S): Maier, Rolf Dieter; Bogusz, Maciej
CORPORATE SOURCE: Inst. Forensic Medicine, Aachen Univ. Technol., Aachen, D-52057, Germany
SOURCE: Journal of Analytical Toxicology (1995), 19(2), 79-83
CODEN: JATOD3; ISSN: 0146-4760
PUBLISHER: Preston Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

AB High-performance ***liquid chromatog.*** with photodiode-array detection (***HPLC***-DAD) provides two identification parameters: retention and UV spectral data. The identification power of these two parameters, expressed in standardized form (retention index and absorption maximum with the highest wavelength), is calculated using two approaches: discriminating power (DP) and mean list length (MLL). Authors' ***HPLC*** database, which comprises data for more than 370 substances, is used as the basis of calcns. The identification power of both parameters applied ***sep.*** is low but increases substantially when the combination of retention and spectral data is applied. Addnl., the DP and MLL values obtained for 56 acidic or neutral and 76 basic drugs examined by means of ***HPLC***-DAD and other anal. methods (thin-layer chromatog., gas chromatog. (GC), and UV) detection) are compared. The online combination of ***HPLC*** retention index values and UV spectra, registered by means of DAD, creates an identification system in which the identification potential is slightly lower than the off-line combination of capillary GC and UV spectroscopy.

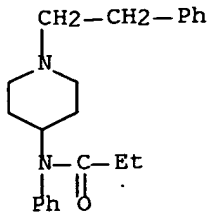
CC 4-2 (Toxicology)
Section cross-reference(s): 1, 9, 64
ST ***HPLC*** toxicol drug analysis forensic
IT Pharmaceutical analysis
(forensic; identification power of standardized ***HPLC*** -photodiode-array detection system for toxicol. anal.)
IT Legal chemistry and medicine
Toxicity
(identification power of standardized ***HPLC***-photodiode-array detection system for toxicol. anal.)
IT Spectrochemical analysis
(UV, identification power of standardized ***HPLC*** -photodiode-array detection system for toxicol. anal.)
IT ***Chromatography, column and liquid***
(high-performance, identification power of standardized ***HPLC*** -photodiode-array detection system for toxicol. anal.)

IT 50-06-6, Phenobarbital, analysis 50-33-9, Phenylbutazone, analysis 50-36-2, Cocaine 50-37-3, LSD 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-78-2, Aspirin 51-55-8, Atropine, analysis 51-71-8, Phenelzine 52-01-7, Spironolactone 52-31-3, Cyclobarbital 52-43-7, Allobarbital 52-53-9, Verapamil 52-86-8, Haloperidol 53-86-1, Indomethacin 54-04-6, Mescaline 54-11-5, Nicotine 56-29-1, Hexobarbital 57-24-9, Strychnine 57-27-2, Morphine, analysis 57-41-0, Phenytoin 57-42-1, Pethidine 57-43-2, Amobarbital 57-44-3, Barbital 58-08-2, Caffeine, analysis 58-15-1, Aminophenazone 58-25-3, Chlordiazepoxide 58-40-2, Promazine 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-46-1, Procaine 60-80-0, Phenazone 60-87-7, Promethazine 62-44-2, Phenacetin 62-67-9, Nalorphine 64-77-7, Tolbutamide 65-45-2, Salicylamide 68-35-9, Sulfadiazine 68-88-2, Hydroxyzine 69-72-7, Salicylic acid, analysis 72-69-5, Nortriptyline 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-68-6, Cyclopentobarbital 76-73-3, Secobarbital 76-74-4, Pentobarbital 76-75-5, Thiopental 76-99-3, Methadone 77-02-1, Aprobarbital 77-07-6, Levorphanol 77-21-4, Glutethimide 77-26-9, Butalbital 77-28-1, Butobarbital 77-36-1, Chlorthalidone 77-65-6, Carbromal 77-66-7, Acecarbromal 77-67-8, Ethosuximide 80-77-3, Chlormezanone 81-07-2, Saccharin 93-14-1, Guaifenesin 94-09-7, Benzocaine 94-24-6, Tetracaine 103-84-4, Acetanilide 113-45-1, Methylphenidate 113-59-7, Chlorprothixene 115-37-7, Thebaine 115-38-8, Methylphenobarbital 122-09-8, Phentermine 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 125-33-7, Primidone 128-62-1, Noscapine 129-20-4, Oxyphenbutazone 130-95-0, Quinine 137-58-6, Lidocaine 146-22-5, Nitrazepam 146-48-5, Yohimbine 151-83-7, Methohexital 155-09-9, Tranylcypromine 299-42-3, Ephedrine 300-62-9, Amphetamine 303-49-1, Clomipramine 357-56-2, Dextromoramide 359-83-1, Pentazocine ***437-38-7***, Fentanyl 438-60-8, Protriptyline 439-14-5, Diazepam 466-99-9, Hydromorphone 469-62-5, Dextropropoxyphene 479-92-5, Propyphenazone 509-86-4, Heptabarbital 519-09-5, Benzoylecgonine 537-46-2, Methamphetamine 548-73-2, Droperidol 561-27-3, Diamorphine 561-86-4, Brallobarbital 604-75-1, Oxazepam 739-71-9, Trimipramine 846-49-1, Lorazepam 846-50-4, Temazepam 963-39-3, Demoxepam 1088-11-5, Nordiazepam 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1668-19-5, Doxepin 1812-30-2, Bromazepam 1893-33-0, Pipamperone 2784-73-8 2898-12-6, Medazepam 2955-38-6, Prazepam 4764-17-4, Mda 10262-69-8, Maprotiline 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 17617-23-1, Flurazepam 22316-47-8, Clobazam 23887-31-2, Clorazepate 26864-56-2, Penfluridol
RL: ANT (Analyte); ANST (Analytical study)
(identification power of standardized ***HPLC***-photodiode-array detection system for toxicol. anal.)

IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(identification power of standardized ***HPLC***-photodiode-array detection system for toxicol. anal.)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)

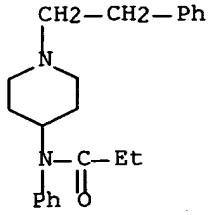


L112 ANSWER 42 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:182309 HCAPLUS Full-text
DOCUMENT NUMBER: 120:182309
TITLE: Tissue distribution of fentanyl and alfentanil in the rat cannot be described by a blood flow limited model
AUTHOR(S): Bjoerkman, Sven; Stanski, Donald R.; Harashima, Hideyoshi; Dowrie, Robert; Harapat, Sandra R.; Wada, D. Russell; Ebling, William F.
CORPORATE SOURCE: Hosp. Pharm., Malmoe Gen. Hosp., Malmoe, S-21401, Swed.
SOURCE: Journal of Pharmacokinetics and Biopharmaceutics (1993), 21(3), 255-79
CODEN: JPBPBJ; ISSN: 0090-466X
DOCUMENT TYPE: Journal
LANGUAGE: English

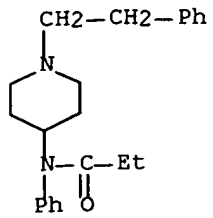
AB Traditionally, physiol. pharmacokinetic models assume that arterial blood flow to tissue is the rate-limiting step in the transfer of drug into tissue parenchyma. When this assumption is made the tissue can be described as a well-stirred single compartment. This study presents the tissue washout concentration curves of the two opioid analgesics fentanyl and alfentanil after simultaneous 1-min i.v. infusions in the rat and explores the feasibility of characterizing their tissue pharmacokinetics, modeling each of the 12 tissues ***sep.***, by means of either a one-compartment model or a unit disposition function. The tissue and blood concns. of the two opioids were measured by gas-***liquid chromatog.*** The well-stirred one-compartment tissue model could reasonably predict the concentration-time course of fentanyl in the heart, pancreas, testes, muscle, and fat, and of alfentanil in the brain and heart only. In most other tissues, the initial uptake of the opioids was considerably lower than predicted by this model. The unit disposition functions of the opioids in each tissue could be estimated by nonparametric numerical deconvolution, using the arterial concentration times tissue blood flow as the input and measured tissue concns. as the response function. The observed zero-time intercepts of the unit disposition functions were below the theor. value of one, and were invariably lower for alfentanil than for fentanyl. These findings can be explained by the existence of diffusion barriers within the tissues and they also indicate that alfentanil is less efficiently extracted by the tissue parenchyma than the more lipophilic compound fentanyl. The individual unit disposition functions obtained for fentanyl and alfentanil in 12 rat tissues provide a starting point for the development of models of intratissue kinetics of these opioids. These submodels can then be assembled into full physiol. models of drug disposition.

CC 1-2 (Pharmacology)
IT ***437-38-7***, Fentanyl 71195-58-9, Alfentanil
RL: BIOL (Biological study)
(tissue distribution of, blood flow limited model in relation to)
IT ***437-38-7***, Fentanyl
RL: BIOL (Biological study)

(tissue distribution of, blood flow limited model in relation to)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



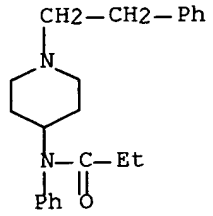
L112 ANSWER 43 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:116930 HCAPLUS Full-text
DOCUMENT NUMBER: 120:116930
TITLE: Determination of impurities in fentanil
AUTHOR(S): Bokovikova, T. N.; Klyuev, N. A.; Gorozhankin, S. K.; Stronova, L. A.; Suranova, A. V.
CORPORATE SOURCE: Gos. NII Standard. Kontrol. Lek. Sredstv, Moscow, Russia
SOURCE: Khimiko-Farmatsevticheskii Zhurnal (1993), 27(7), 58-60
CODEN: KHFZAN; ISSN: 0023-1134
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Two synthetic impurities, 1-(2-phenylethyl)-4-(N-acetyl-N-phenylamino)piperidine (2.3%) and 1-(2-phenylethyl)-4-(N-butyryl-N-phenylamino)piperidine (1.7%), were determined in fentanyl by ***HPLC*** and mass spectrometry, after gas chromatog. ***separation***
CC 64-3 (Pharmaceutical Analysis)
Section cross-reference(s): 80
ST fentanyl impurity ***HPLC*** mass spectrometry; chromatog mass spectrometry fentanyl impurity
IT ***437-38-7***, Fentanil
RL: ANST (Analytical study)
(determination of impurities and, by ***HPLC*** and mass spectrometry)
IT 976-65-8 1169-70-6
RL: ANT (Analyte); ANST (Analytical study)
(determination of, as fentanil impurity, by ***HPLC*** and mass spectrometry)
IT ***437-38-7***, Fentanil
RL: ANST (Analytical study)
(determination of impurities and, by ***HPLC*** and mass spectrometry)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 44 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:584177 HCAPLUS Full-text
DOCUMENT NUMBER: 117:184177
TITLE: High-performance ***liquid chromatographic*** assay of fentanyl in human plasma
AUTHOR(S): Zhu, Zhu; Chen, Lanying
CORPORATE SOURCE: Dep. Pharm., Beijing Union Hosp., Beijing, 100 730, Peop. Rep. China
SOURCE: Zhongguo Yiyuan Yaoxue Zazhi (1992), 12(3), 101-3
CODEN: ZYYAEP; ISSN: 1001-5213
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB An ***HPLC*** method for the determination of fentanyl in human plasma was described. The ***separation*** of fentanyl, alfentanil and sufentanil was also reported. The ***HPLC*** method is linear in the range of 1-200 ng/mL for fentanyl. The within-day and between-days variation coefficient was 8.08 and 9.56%, resp. The detection limit was 0.25 ng. Total recovery was 90.6%. Using phosphate buffer as mobile phase and detection wavelength at 195 nm, alfentanil, fentanyl, and sufentanil could be successfully ***separated*** with a retention time of 7.2, 10.7, and 13.5 min, resp. This method is suitable for pharmacokinetic studies of these drugs.

CC 1-1 (Pharmacology)
ST fentanyl alfentanil sufentanil blood ***HPLC; liq chromatog*** fentanyl alfentanil sufentanil blood
IT Blood analysis
(alfentanil and fentanyl and sufentanil determination in human, by ***HPLC***)
IT 56030-54-7, Sufentanil
RL: ANST (Analytical study)
(determination of alfentanil and fentanyl and, in human blood plasma by ***HPLC***)
IT ***437-38-7***, Fentanil
RL: ANST (Analytical study)
(determination of alfentanil and sufentanil and, in human blood plasma by ***HPLC***)
IT 71195-58-9, Alfentanil
RL: ANST (Analytical study)
(determination of fentanyl and sufentanil and, in human blood plasma by ***HPLC***)
IT ***437-38-7***, Fentanil
RL: ANST (Analytical study)
(determination of alfentanil and sufentanil and, in human blood plasma by ***HPLC***)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 45 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:137547 HCAPLUS Full-text
DOCUMENT NUMBER: 114:137547
TITLE: Micellar electrokinetic capillary chromatography of illicit drug substances
AUTHOR(S): Weinberger, Robert; Lurie, Ira S.
CORPORATE SOURCE: Appl. Biosyst., Inc., Ramsey, NJ, 07446, USA
SOURCE: Analytical Chemistry (1991), 63(8), 823-7
CODEN: ANCHAM; ISSN: 0003-2700
DOCUMENT TYPE: Journal
LANGUAGE: English

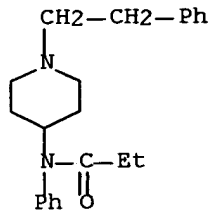
AB Micellar electrokinetic capillary chromatog. (MECC) was found to give significantly greater efficiency, selectivity, peak symmetry, and speed compared to ***HPLC*** for the determination of illicit drug substances. For a complex mixture consisting of acidic and neutral impurities present in an illicit heroin seizure sample, MECC resolved at least twice as many peaks as ***HPLC***. MECC permitted the anal. of heroin and its basic impurities, the common adulterants phenobarbital and methaqualone, in approx. one-third the anal. time of ***HPLC*** with superior resolution Illicit cocaine, and its basic impurities, were analyzed by MECC without the significant tailing that is found with reversed-phase ***liquid chromatog.*** using bonded-phase columns. Other drugs investigated via MECC include opium alkaloids, amphetamines, hallucinogens, barbiturates, benzodiazepines, and cannabinoids. All of these ***sepns***. were accomplished with 25-100-cm capillaries (length to detector) by using a hydroorg. buffer consisting of 85 mM sodium dodecyl sulfate, 8.5 mM phosphate, 8.5 mM borate, and 15% acetonitrile at a pH of 8.5. Detection was by UV absorption at 210 nm. Due to its speed, high resolving power, and the probability that all compds. must elute at or before tmc (micellar aggregate migration time), MECC is well suited for general drug screening.

CC 4-2 (Toxicology)
Section cross-reference(s): 1

IT ***Chromatography, column and liquid***
(capillary, electrokinetic, micellar, of illicit drug substances)

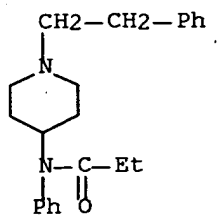
IT 50-06-6, Phenobarbital, analysis 50-36-2, Cocaine 50-37-3, LSD 54-04-6, Mescaline 57-27-2, Morphine, analysis 58-74-2, Papaverine 67-52-7D, Barbituric acid, derivs. 71-68-1, Dilaudid 72-44-6, Methaqualone 76-57-3, Codeine 77-10-1, PCp 122-09-8, Phentermine 128-62-1, Noscapine 129-00-0, Pyrene, analysis 300-62-9, Amphetamine 300-62-9D, Amphetamine, derivs. ***437-38-7***, Fentanyl 438-41-5, Librium 439-14-5 519-09-5, Benzoylecgonine 520-52-5, Psilocybine 520-53-6, Psilocine 521-35-7, Cannabinol 537-46-2, Methamphetamine 561-27-3, Heroin 846-49-1 1972-08-3 2784-73-8, O6-Monoacetylmorphine 4764-17-4, MDA 5140-28-3, O3-Monoacetylmorphine 6703-27-1, Acetylcodeine 12794-10-4D, Benzodiazepine, derivs. 13956-29-1, Cannabidiol 17617-23-1, Flurazepam 40158-98-3, LAMPA 42542-10-9,

MDMA 50763-20-7, trans-Cinnamoylcocaine 50763-21-8, cis-Cinnamoylcocaine
RL: ANT (Analyte); ANST (Analytical study)
(determination of, by micellar electrokinetic capillary chromatog.)
IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(determination of, by micellar electrokinetic capillary chromatog.)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 46 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:491816 HCAPLUS Full-text
DOCUMENT NUMBER: 111:91816
TITLE: Screening and confirmation of drugs in horse urine by using a simple column extraction procedure
AUTHOR(S): Singh, Ashok K.; Ashraf, M.; Granley, K.; Mishra, U.; Rao, M. Madhusudana; Gordon, Brad
CORPORATE SOURCE: Coll. Vet. Med., Univ. Minnesota, St. Paul, MN, 55108, USA
SOURCE: Journal of Chromatography (1989), 473(1), 215-26
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A simple and reproducible column (Clean Screen-DAU, copolymeric bonded-phase silica column) extraction procedure was described for the screening and confirmation of drugs in horse urine. The recovery of drugs by the column extraction was better than or comparable to the recovery of the liquid-liquid extraction, which is commonly used in the equine anal. labs. The column extraction provided broad coverage of drugs, ***sep.*** exts. into three fractions (acidic/neutral, steroids, and basic), produced a cleaner extract, and eliminated the need for special liquid-liquid extraction procedures for different drugs. The column extract was cleaner and did not contain impurities, whereas, the liquid-liquid extract was relatively impure and the extract required further thin-layer chromatog. cleanup. The column extraction procedure was used to confirm illegal doping by the presence of several potent drugs, such as fentanyl, etorphine, and mazindol.
CC 4-2 (Toxicology)
IT ***Chromatography, column and liquid***
(in drugs of abuse determination in horse urine)
IT 50-33-9, Phenylbutazone, analysis 50-36-2, Cocaine 61-00-7, Acepromazine 137-58-6, Lidocaine 300-62-9, Amphetamine ***437-38-7***, Fentanyl 439-14-5, Diazepam 521-35-7 537-46-2, Methamphetamine 7361-61-7, Xylazine 14521-96-1, Etorphine 22204-53-1, Naproxen 22232-71-9, Mazindol
RL: ANT (Analyte); ANST (Analytical study)

(determination of, in horse urine, forensic)
IT ***437-38-7***, Fentanyl
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in horse urine, forensic)
RN 437-38-7 HCAPLUS
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 47 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:523899 HCAPLUS Full-text
DOCUMENT NUMBER: 109:123899
TITLE: Analyzing normetabolites of the fentanyls by gas chromatography/electron capture detection
AUTHOR(S): Hammargren, W. R.; Henderson, G. L.
CORPORATE SOURCE: Sch. Med., Univ. California, Davis, CA, 95616, USA
SOURCE: Journal of Analytical Toxicology (1988), 12(4), 183-91
CODEN: JATOD3; ISSN: 0146-4760
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A selective and sensitive gas-***liquid chromatog.*** (GC) method has been developed for analyzing the normetabolites of fentanyl and 3-methylfentanyl in the urine. The method employs differential pH extraction of 1 mL samples, extractive acylation with pentafluoropropionic anhydride (PFPA), GC ***separation*** on a fused-silica capillary column (DB-1701), and detection by electron capture detector (ECD) or mass spectroscopy (MS). Limit of sensitivity for this method is 2 ng/mL for norfentanyl (NF) and nor-3-methylfentanyl (N-3-MF) using a 1-mL urine sample and a 2-μL injection from a final volume of 20 μL. Within-run precision, expressed as the coefficient of variation (CV), was 14% and 5% for 4 ng/mL and 16 ng/mL of NF and 9% and 4% for the same concns. of N-3-MF. Between-run precision was 30% and 12% for NF and 11% and 10% for N-3-MF, at 4 ng/mL and 16 ng/mL, resp. Metabolites are stable in urine for at least one month at room temperature (25°) or -20°. PFP-derivs. of the metabolites were confirmed by the high-resolution MS in the electron-impact mode. Three characteristic ions for each metabolite were identified-m/z 392 (mol. ion), m/z 336 (loss of propionyl), and m/z 244 (loss of propionanilide) for N-3-MF-PFP and m/z 378 (mol. ion), m/z 322 (loss of propionyl), and m/z 230 (loss of propionanilide) for NF-PFP, suitable for use in GC/MS with selected ion monitoring as a complimentary confirming technique. This method was validated by analyzing urine samples from individuals suspected of using fentanyl or 3-methylfentanyl. Concns. of the parent drugs, as determined by RIA, were approx. 1 ng/mL, while concns. of the normetabolites, as determined by PFPA derivatization and GC/ECD, were generally 10-fold higher. Thus, this GC/ECD method for the normetabolites of the fentanyls, when coupled with the RIA screening technique, may be used in urine testing to detect abuse of both the licit and illicit fentanyls.

CC 4-2 (Toxicology)

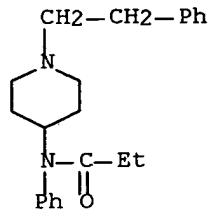
Section cross-reference(s): 1

IT ***437-38-7D***, Fentanyl, derivs.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, normetabolites determination in urine of humans by gas chromatog.
with electron capture or mass spectroscopy in)

IT ***437-38-7D***, Fentanyl, derivs.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, normetabolites determination in urine of humans by gas chromatog.
with electron capture or mass spectroscopy in)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 48 OF 56 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1984:497748 HCAPLUS Full-text

DOCUMENT NUMBER: 101:97748

ORIGINAL REFERENCE NO.: 101:14879a,14882a

TITLE: Reversed-phase high-performance ***liquid chromatographic separation*** of fentanyl homologs and analogs. II. Variables affecting hydrophobic group contribution

AUTHOR(S): Lurie, I. S.; Allen, A. C.

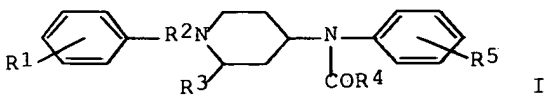
CORPORATE SOURCE: Special Test. Res. Lab., Drug Enforcement Adm., McLean, VA, 22102-3494, USA

SOURCE: Journal of Chromatography (1984), 292(2), 283-94
CODEN: JOCRAM; ISSN: 0021-9673

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB The effects of organic modifier, stationary phase, hydrophobic substitution, and temperature on the group contribution values for fentanyl homologs and analogs I (R1 and R3 = H, or Me; R2 = CH2, (CH2)2, or CH2CHMe, (CH2)3, etc.,

R4 = Me or Et; R5 = H, F, or Me) were studied. Using equations relating group contribution to mol. connectivity, it was found that hydrophobic selectivity is approx. independent of mobile phase composition for mixts. commonly employed in solvent optimization schemes based on overlapping resolution mapping. Similarly, hydrophobic selectivity was also identical on both silica-based Partisil 10-ODS-3 and polymer-based PRP-1 columns under normalized time conditions. In contrast, hydrophobic selectivity depended on the position of methylene substitution on the parent fentanyl mol. and the type of substituent. For all mobile phases studied there is a small decrease in group contribution values with increases in temperature

CC 64-3 (Pharmaceutical Analysis)
Section cross-reference(s): 66

ST fentanyl analog ***HPLC***; hydrophobic substitution fentanyl analog; org modifier ***HPLC*** fentanyl analog; stationary phase ***HPLC*** fentanyl analog; mobile phase ***HPLC*** fentanyl analog; chromatog liq fentanyl analog

IT Hydrophobicity
(of fentanyl analogs, ***liquid chromatog.*** in relation to)

IT Silica gel, properties
RL: PRP (Properties)
(stationary phase, in fentanyl analogs reversed-phase ***HPLC***, hydrophobic selectivity of)

IT ***Chromatography, column and liquid***
(high-performance, reversed-phase, of fentanyl analogs, hydrophobic group contribution in)

IT Molecular structure-property relationship
(***liquid chromatog.***, of fentanyl analogs)

IT 67-56-1, uses and miscellaneous 75-05-8, uses and miscellaneous 109-99-9, uses and miscellaneous
RL: USES (Uses)
(buffered mobile phase containing, in reversed-phase ***HPLC*** of fentanyl analogs, hydrophobic selectivity in relation to)

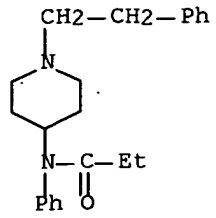
IT ***437-38-7D***, analogs 1237-52-1 1474-02-8 1640-10-4 1838-67-1 2141-47-1 3258-84-2 42045-77-2 47480-47-7 59708-54-2 79146-56-8 79704-88-4 90736-10-0 90736-11-1 90736-12-2 90736-13-3 90736-14-4 90736-15-5 90736-16-6 90736-17-7 90736-18-8 90736-19-9 90736-20-2 90736-21-3 90736-22-4 90736-23-5
RL: ANT (Analyte); ANST (Analytical study)
(chromatog. of, reversed-phase high-performance liquid, hydrophobic group contribution in)

IT 9003-70-7
RL: ANST (Analytical study)
(stationary phase, in reversed-phase ***HPLC*** of fentanyl homologs, hydrophobic group contribution in relation to)

IT ***437-38-7D***, analogs
RL: ANT (Analyte); ANST (Analytical study)
(chromatog. of, reversed-phase high-performance liquid, hydrophobic group contribution in)

RN 437-38-7 HCAPLUS

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 49 OF 56 USPATFULL on STN

ACCESSION NUMBER: 2007:265452 USPATFULL Full-text

TITLE: Active agent delivery systems and methods for protecting and administering active agents

INVENTOR(S): Mickle, Travis, Charlottesville, VA, UNITED STATES
Krishnan, Suma, Blacksburg, VA, UNITED STATES
Moncrief, James Scott, Christiansburg, VA, UNITED STATES
Lauderback, Christopher, Blacksburg, VA, UNITED STATES
Piccariello, Thomas, Blacksburg, VA, UNITED STATES
Kirk, Randal, Radford, VA, UNITED STATES

PATENT ASSIGNEE(S): New River Pharmaceuticals Inc., Radford, VA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2007232529	A1	20071004	<--
APPLICATION INFO.:	US 2004-923088	A1	20040823 (10)	<--

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2003-US5524, filed on 24 Feb 2003, PENDING Continuation-in-part of Ser. No. US 2001-933708, filed on 22 Aug 2001, PENDING Continuation-in-part of Ser. No. US 2000-642820, filed on 22 Aug 2000, GRANTED, Pat. No. US 6716452 Continuation-in-part of Ser. No. US 2003-727565, filed on 5 Dec 2003, PENDING Continuation-in-part of Ser. No. US 2002-156527, filed on 29 May 2002, PENDING Continuation-in-part of Ser. No. US 2002-156527, filed on 29 May 2002, PENDING Continuation-in-part of Ser. No. US 2001-987458, filed on 14 Nov 2001, ABANDONED Continuation-in-part of Ser. No. US 2001-988071, filed on 16 Nov 2001, ABANDONED Continuation-in-part of Ser. No. WO 2001-US43089, filed on 14 Nov 2001, PENDING Continuation-in-part of Ser. No. WO 2001-US43117, filed on 16 Nov 2001, PENDING Continuation-in-part of Ser. No. WO 2001-US43115, filed on 16 Nov 2001, PENDING

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	US 2000-248767P	20001116 (60)
	US 2000-248787P	20001116 (60)
	US 2000-248774P	20001116 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUNTON & WILLIAMS LLP, INTELLECTUAL PROPERTY DEPARTMENT, 1900 K STREET, N.W., SUITE 1200, WASHINGTON, DC, 20006-1109, US
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1-56
NUMBER OF DRAWINGS: 45 Drawing Page(s)
LINE COUNT: 9745
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to active agent delivery systems and more specifically to compositions that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for administering conjugated active agent compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 2004-923088 A1 20040823 (10) <--
SUMM . . . N-carboxyanhydrides. In another embodiment, the peptide can be prepared through a fermentation process of recombinant microorganisms followed by harvesting and ***purification*** of the appropriate peptide. Alternatively, if a specific sequence of amino acids is desired, an automated peptide synthesizer can be. . .
SUMM In a preferred embodiment neither the carrier or the conjugate are used for assay ***purification,*** binding studies or enzyme analysis.
DETD . . . Estradiol; Norethindrone
Ethinyl Estradiol; Norgestimate
Ethinyl Estradiol; Norgestrel
Ethylmorphine
Etidronate Disodium
Etodolac
Etoposide
Etoricoxib
Exendin-4
Famciclovir
Famotidine
Felodipine

Fenofibrate
Fenretinide
Fentanyl
Fexofenadine Hydrochloride
Filgrastim SD01
Finasteride
Flecainide Acetate
Fluconazole
Fludrocortisone Acetate
Flumazenil
Fluorouracil
Fluoxetine
Flutamide
Fluticasone
Fluvastatin
Fluvoxamine Maleate
Follitropin Alfa/Beta

. . .

DETD . . . stirred for several hours at room temperature, the urea by-product filtered off, and the product precipitated out in ether and ***purified*** using gel permeation chromatography (GPC) or dialysis.

DETD . . . room temperature for several hours. The product is then precipitated out in ether. The crude product is suitably deprotected and ***purified*** using GPC.

DETD . . . The resulting dark solution was stirred overnight. Solvent was then removed, NaHCO.sub.3 (saturated solution) added and the crude product was ***purified*** using ultrafiltration (YM1) to obtain Furosemide-pSer (0.101 g) as a dark green solid.

DETD . . . the organics). The organics were dried with anhyd. MgSO.sub.4, filtered and the solvent removed by rotary evaporation. The residue was ***purified*** by flash chromatography (SiO.sub.2 1:0-60:1-40:1-30:1-20:1-10:1) to provide Enalipril-Glu(OtBu)Glu(OtBu)OtBu as a yellowish gum (0.231 g, 54%): R.sub.f 0.43 (9:1 CHCl.sub.3:MeOH+1. . .

DETD . . . stirred for several hours at room temperature, the urea by-product filtered off, and the product precipitated out in ether and ***purified*** using GPC or dialysis.

DETD . . . (Glu).sub.5-14-cephalexin (SEQ ID NO: 2). Other chain-lengths may be present but they are not clearly visible in the MALDI spectra. ***Reversed-phase HPLC*** (265 nm detection, C18 column, 16%MeOH/4%THF/80%water mobile phase) indicated that no free cephalexin was present in the isolated material. "Water" in the ***HPLC*** actually refers to an aqueous buffer of 0.1% heptanesulfonic acid and 1.5% triethylamine.

DETD . . . evaporation under reduced pressure, yielding light brown oil. The oil was dried on the vacuum manifold and the product was ***purified*** by column chromatography on silica gel using EtOAc/Hexanes 1:5 to 1:4 solvent system. The product fractions were pooled and solvent. . .

DETD . . . evaporation under reduced pressure, yielding light brown oil. The oil was dried on the vacuum manifold and the product was ***purified*** by column chromatography on silica gel using EtOAc/Hexanes 1:5 to 1:4 solvent system. The product fractions were pooled and solvent. . .

DETD . . . ambient temperatures for 18 hours. Reaction was quenched with sat. NaHCO3 (25 ml) and solvent was removed. Crude material was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 70 0.1% TFA-water/30 0.1% TFA-MeCN→0/100 0-15 min.; 30 ml/min.). Solid. . .

DETD . . . NMM followed by Boc-Ala-OSu. The solution was stirred at ambient temperatures for 18 hours. Solvent was removed. Crude material

was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 100 water/0 0.1% TFA-MeCN→0/100; 30 ml/min.). Solid was collected as. . .

DETD . . . NMM followed by Boc-Gly-Gly-OSu. The solution was stirred at ambient temperatures for 18 hours. Solvent was removed. Crude material was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 90 water/10 0.1% TFA-MeCN→0/100; 30 ml/min.). Solid was collected as. . .

DETD . . . NMM followed by Boc-Gly-Gly-OSu. The solution was stirred at ambient temperatures for 18 hours. Solvent was removed. Crude material was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 85 water/15 0.1% TFA-MeCN→50/50; 30 ml/min.). Solid was collected as. . .

DETD . . . methanol or i-propanol was then added and the resulting solid was collected and dissolved in NaHCO.sub.3(sat.). The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation, methanol precipitation, acetone precipitation or removal of water under. . .

DETD . . . for 6 hours and heated at 70° C. for 12 hours. Solvent was then removed and the crude product was ***purified*** over silica gel (100% CHCl.sub.3) to obtain Boc-Glu(AZT)-OtBu (1.09 g, 1.91 mmol, 51%) as a yellow foam. (See also, FIG.. . .

DETD . . . dried mixture was-added water (100 mL) and a precipitate of unreacted acyclovir formed. Solid was centrifuged and the supernatant was ***purified*** using ultrafiltration (YM1 membrane). Approximately 300 mL water was allowed to pass through the membrane. NMR has shown an unexpected. . .

DETD . . . (25 mL). A solid precipitate formed which was both drug-conjugate and free fexofenadine. Water was acidified and all solids dissolved. ***Purification*** using ultrafiltration (YM1 followed by YM3) and size exclusion chromatography using Sephadex-25 at pH 7 yielded poly-glu(fexofenadine) (0.010 g) as. . .

DETD Preparation was similar to poly-Glu(zalcitabine). ***Purification*** using ultrafiltration (YM1) yielded poly-Glu(stavudine) (0.089 g) as a white solid. (See FIG. 20).

DETD . . . evaporation. Water was then added and the resulting solid was collected and dissolved in saturated NaHCO.sub.3. The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation (1.15 g, 48%). (See FIG. 21).

DETD Preparation was similar to poly-glu(zalcitabine). ***Purification*** using ultrafiltration (YM1) yielded poly-Glu(metronidazole) (0.326 g) as a yellow solid. (See FIG. 22).

DETD . . . evaporation. Water was then added and the resulting solid was collected and dissolved in saturated NaHCO.sub.3. The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation (0.965 g, 35%). (See also, FIG. 23).

DETD . . . was allowed to heat to reflux and stirred at reflux overnight. Solvent was then removed and the crude compound was ***purified*** over silica gel (50-75% ethyl acetate in hexanes) to obtain Boc-Glu(Acetaminophen)-OtBu (0.432 g, 0.900 mmol, 72%).

DETD . . . added. The reaction was stirred for 60 hours and filtered. The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (10:1-0:1 hexane:EtOAc) to provide the target as a clear film (0.256 g, 31%).

DETD . . . was stirred for 1 hour with trifluoroacetic acid (1.5 mL). The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (8:1 CHCl.sub.3:MeOH) to yield a clear film.

DETD . . . (0.22 mL, 1.98 mmol). The solution was then refluxed for 48 hours. Solvent was then removed and crude product was ***purified*** over silica gel (25-50% ethyl acetate in hexanes). Two major products were isolated, one with R.sub.f=2-3, Boc-Glu(dipyrimadole)-OtBu, (0.57 g) and. . .

DETD . . . (100 mL) was then added and the resulting solid was collected and dissolved in saturated NaHCO.sub.3. The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation as a green solid (0.678 g, 32%).

DETD . . . whereupon the solution was filtered to remove the white precipitate and the solvent removed by rotary evaporation. The residue was ***purified*** by flash chromatography (10:1-2:1 hexane:EtOAc) to provide the succinimidyl ester as a clear oil (1.0 g, 59%).

DETD . . . with 2 mL CH.sub.2Cl.sub.2. The aqueous layer was dried and the residue dissolved in 1 mL H.sub.2O. The solution was ***purified*** by SEC (G-15, 10 mL dry volume) and eluted with water. Those fractions containing conjugate were combined and dried to. . .

DETD . . . ml). Organic layer was dried with MgSO.sub.4 and filtered. Solvent was removed and solid was dried over vacuum. Product was ***purified*** using prep. ***HPLC*** [Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: (100 0.1% TFA-water/0 0.1% TFA-MeCN→80/20) 0-10 min. (80/20→50/50) 10-25 min.;. . .

DETD . . . stir over night at room temperature under argon. The following morning, 2.5 mL of the reaction mixture was transferred to ***separate*** flask (Flask B). T4-NCA (27 mg, 0.03 mmol) was added to the original flask (Flask A), and both solutions were. . .

DETD For Those Conjugates That Used a Protected NCA an Additional, ***Separate*** Deprotection Step was Necessary:

DETD . . . residue was dried in vacuum to provide Trp(Boc).sub.15-T4 (SEQ ID NO: 13) as a brown solid. This material was further ***purified*** by ultrafiltration (Amicon regenerated cellulose, YM1, NMWL 1000, wash with 30 mL pH 5 H.sub.2O) to provide [Trp(Boc)].sub.15-T4 (SEQ ID. . .

DETD . . . in the synthesis of [Glu].sub.15-L-DOPA (SEQ ID NO: 3) except 0.439 grams of GluNCA were used. The final yield of ***purified*** material was 0.007 grams.

DETD . . . was removed by rotary evaporation to provide the deprotected polymer as a brown solid (0.262 g, 91%) which was further ***purified*** by ultrafiltration (Amicon regenerated cellulose, YM1, NMWL 1000, wash with 30 nL pH 5 H.sub.2O).

DETD . . . N-dimethyl-4-aminopyridine (0.119 g, 1.0 mmol). After stirring for 18 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (30:1-8:1 CHCl.sub.3:CH.sub.3OH with 1 drop HOAc/100 mL eluent) to provide the target as a white solid (0.242. . .

DETD . . . N-dimethyl-4-aminopyridine (0.217 g, 1.8 mmol). After stirring for 16 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (30:1-8:1 CHCl.sub.3:CH.sub.3OH with 1 drop HOAc/100 mL eluent) to provide the target as a white solid (0.473. . .

DETD . . . N-dimethyl-4-aminopyridine (0.051 g, 0.42 mmol). After stirring for 21 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (12:1-0:1 hexane:EtOAc) to provide the target as a white solid (0.187 g, 55%): R.sub.f(1:1 hexane:EtOAc) 0.95; .sup.1H. . .

DETD . . . N-dimethyl-4-aminopyridine (0.051 g, 0.42 mmol). After stirring for 18.5 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (12:1-0:1 hexane:EtOAc) to provide the target as a white solid contaminated with

1-hexadecanol (0.348 g, 90%): R.sub.f(3:1. . .

DETD . . . This suspension was cooled to 4° C., filtered and dried by high vacuum for 5 hours. This material was further ***purified*** by ultrafiltration (3,000 MW) filter using saturated sodium bicarbonate as a diluent. The product was dissolved in 10 mL of. . .

DETD . . . filtered through glasswool and washed with 20 mL EtOAc. The water was removed by lyophilization and the off white residue ***purified*** by flash chromatography (C18 CH.sub.3OH) to provide roughly a 1:1 mixture of TeocT3-β-CD (R.sub.f7:7:5:4 EtOAc:2-propanol:NH.sub.4OH:H.sub.2O) 0.64) and unmodified β-CD (R.sub.f. . .

DETD . . . overnight). The product can be isolated from the solution by pouring it into water and filtering. The product can be ***purified*** using GPC or dialysis.

DETD . . . stirred for several hours at room temperature, the urea by-product filtered off, and the product precipitated out in ether and ***purified*** using GPC or dialysis.

DETD . . . cooling, reaction was placed in ether and solid was collected by filtration. Solid was suspended in pH 8 water and ***purified*** using ultrafiltration. Product was filtered and dried.

DETD . . . then allowed to stir at 20° C. for 8 hours. The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (8:1-1:1 hexane:EtOAc) to provide the conjugate as a clear film (0.038 g, 11%).

DETD . . . under argon whereupon the solution was filtered through glass wool and the solvent removed by rotary evaporation. The residue was ***purified*** by flash chromatography (30:1-8:1 CHCl.sub.3:CH.sub.3OH) to provide the peracylated statin as a white solid (0.118 g).

DETD . . . water (3+100 mL). The organic layer was dried over MgSO.sub.4 and solvents were removed under reduced pressure. Crude product was ***purified*** over silica gel (0-10% MeOH in CHCl.sub.3) to obtain the ketal conjugate (0.010 g) in a 1:1 mixture with free. . .

DETD . . . added and the mixture washed with 5 mL saturated NaCl. The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (15:1:0-10:1:0-100:10:1 CHCl.sub.3:MeOH:HOAc) to provide the target as a white solid (23%).

DETD . . . was added and the reaction stirred 24 more hours. The solvent was removed by rotary evaporation and the residue repeatedly ***purified*** by flash chromatography to provide the target as a white solid (7%).

DETD . . . to remove gross particulate matter. Any remaining particulate was filtered with a 0.2 μm nylon syringe filter (Whatman) prior to ***HPLC*** analysis.

DETD Enzyme digested conjugates were analyzed for the presence of unconjugated active agent by ***reversed phase HPLC*** (C18, 4.6+250 mm, 5 μm, 300 A) using the following conditions: mobile phase--Lotus buffer (4.5 mL of H.sub.3PO.sub.4, 8.8 mL. . .

DETD Polyserine-naltrexone conjugates were tested in male Sprague Dawley rats (.about.250 g). Defined doses were delivered orally in gelatin capsules containing ***purified*** dry powder polyserine-naltrexone conjugates or naltrexone. No excipients were added to the capsules.

DETD Polyserine-naltrexone conjugates were tested in Sprague-dawley rats (.about.250 g). Defined doses were delivered orally in gelatin capsules containing ***purified*** dry powder polyserine-naltrexone conjugates or naltrexone. No excipients were added to the capsules.

DETD . . . was removed from the monlayers and concentrated on SP-18

columns. Concentrated samples were analyzed for the presence of naltexone by ***reverse phase HPLC***. Each Polyserine-naltrexone conjugate showed significant release of free naltrexone from the polymer conjugate in three ***separate*** samples. In conclusion, Caco-2 cellular enzymes affected release of naltrexone from Polyserine-naltrexone conjugates BB-272 and BB-301. Release of carbonate linked. . .

DETD . . . amines, amides, alcohols, or acids) or may be made up of a short chain of either amino acids or carbohydrates. ***Fentanyl***

DETD ***Fentanyl*** is a known pharmaceutical agent that is used in the treatment of pain. It is both commercially available and readily. . . published synthetic schemes by those of ordinary skill in the art. Its structure is: ##STR412## In the present invention, the ***fentanyl*** or modified ***fentanyl*** is covalently attached to the peptide via a linker. This linker may be a small molecule containing 2-6 carbons and. . .

L112 ANSWER 50 OF 56 USPATFULL on STN
ACCESSION NUMBER: 2007:141477 USPATFULL Full-text
TITLE: Prodrugs of active agents
INVENTOR(S): Jenkins, Thomas E., La Honda, CA, UNITED STATES
PATENT ASSIGNEE(S): Pharmacofore, Inc. (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2007123468	A1	20070531		<--
APPLICATION INFO.:	US 2006-508042	A1	20060821	(11)	<--

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-711438P	20050819 (60)
	US 2005-711862P	20050825 (60)
	US 2006-760762P	20060120 (60)
	US 2006-799532P	20060510 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORGAN, LEWIS & BOCKIUS, LLP, ONE MARKET SPEAR STREET TOWER, SAN FRANCISCO, CA, 94105, US
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 2805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed herein are prodrugs of active agents which contain at least one amine, phenol, carboxylic acid, or thiol functionality. Also disclosed herein are methods of making prodrugs of active agents, pharmaceutical compositions of prodrugs of active agents and methods of using prodrugs of active agents and pharmaceutical compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AI US 2006-508042 A1 20060821 (11) <--

SUMM . . . of the prodrug includes a spacer group and a cleavable moiety where the spacer group may electronically decouple and/or sterically ***separate*** the active agent from the cleavable moiety. Accordingly, a prodrug disclosed herein generally comprises an active agent attached through a. . .

DETD . . . the description of the compounds herein. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using ***separation*** techniques or chiral

synthesis techniques well known to the skilled artisan. The compounds may also exist in several tautomeric forms. . .

DETD . . . promoiety includes a spacer group and a cleavable moiety where the spacer group may, inter alia, electronically decouple and/or physically ***separate*** the active agent from the cleavable moiety. Accordingly, a prodrug disclosed herein generally comprises an active agent attached through a. . .

DETD . . . codeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone, naltrexone, nalbuphine, butorphanol, nalorphine, alfentanil, buprenorphine, carfentanil, codeine, diacetylmorphine, dihydrocodeine, dihydroetorphine, diprenorphine, etorphine, ***fentanyl***, levomethadyl actetate hydrochloride, lofentanil, meperidine, methadone, morphine, naloxone, methyl naltrexone, beta-hydroxy 3-methylfentanyl, N-methylnaltrexone, normorphine, propoxyphene, remifentanil, sufentanil, tilidine, thebaine, nalmefene,. . .

DETD . . . codeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone, naltrexone, nalbuphine, butorphanol, nalorphine, alfentanil, buprenorphine, carfentanil, codeine, diacetylmorphine, dihydrocodeine, dihydroetorphine, diprenorphine, etorphine, ***fentanyl***, levomethadyl actetate hydrochloride, lofentanil, meperidine, methadone, morphine, naloxone, methylnaltrexone, beta-hydroxy 3-methylfentanyl, N-methylnaltrexone, normorphine, propoxyphene, remifentanil, sufentanil, tilidine, thebaine, nalmefene, neopine, penomorphone or tramadol. In some of any of the above embodiments, X is morphine, ***fentanyl***, codeine, diacetylmorphine, etorphine, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone, naltrexone, nalbuphine, butorphanol or nalorphine. In other of any of the above. . .

DETD . . . to stir overnight at room temperature. The reaction was then diluted with ethyl acetate (5 ml) and transferred to a ***separatory*** fuinnel and washed with water (3+20 ml), brine (1+10 ml), dried over Na.sub.2SO.sub.4 then filtered and concentrated to yield 330 mgs of a crude oil which solidified upon standing. The crude solid was ***purified*** using flash chromatography employing ethyl acetate/hexane (1:1) as the eluting solvent to yield 130 mgs of desired amide B. The. . .

DETD . . . organic layers were dried over Na2SO4, filtered, and concentrated to yield 0.9 g of crude oil. The crude oil was ***purified*** via flash chromatography using ethyl acetate: hexane (1:1) as the eluting solvent to yield 670 mg of desired benzyl chloride. . .

DETD . . . and concentrated under reduced pressure to yield 570 mgs of the desired TFA protected codeine quaternary salt (97% pure by ***HPLC*** analysis). 4.1 mg of this material was deprotected via exposure to an aqueous solution of K.sub.2CO.sub.3 (4.0 mg) in water. . .

DETD . . . above solution. The reaction mixture was stirred for 2 hours; the solvents were removed in vacuum and the product was ***purified*** by prep ***HPLC*** (acetonitrile gradient) yielding 10 mg (42%) of quaternary salt G. MS: found 561.2, for C.sub.31H.sub.41N.sub.6O.sub.4.sup.+ calculated 561.32.

DETD . . . the reaction proceeds 50 μL aliquots are removed at specific time points, quenched into 100 μL acetonitrile, and analyzed by ***HPLC*** for the disappearance of prodrug and/or the appearance of parent (hydrocodone). This concentration of trypsin (5 μL/mL of a 2.5. . .

DETD . . . opioid prodrug Z remaining after a 30 minute incubation at room temperature with increasing amounts of trypsin as measured by

reverse phase HPLC. FIG. 1B shows the appearance of hydrocodone after a 30 minute incubation at room temperature with increasing amounts of trypsin as measured by ***reverse phase HPLC***.

CLM What is claimed is:

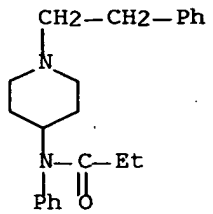
. . . diacetylmorphine, etrophine, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone, naltrexone, nalbuphine, butorphanol, nalorphine, alfentanil, buprenorphine, carfentanil, codeine, diacetylmorphine, dihydrocodeine, dihydroetorphine, diprenorphine, etorphine, ***fentanyl***, levomethadyl actetate hydrochloride, levorphanol, lofentanil, meperidine, methadone, morphine, naloxone, naltrexone, methyl naltrexone, beta-hydroxy 3-methylfentanyl, N-methylnaltrexone, oxymorphone, normorphine, propoxyphene, remifentanil, sufentanil,. . .

IT 51-64-9DP, Dextroamphetamine, prodrugs 57-27-2DP, Morphine, prodrugs, preparation 57-42-1DP, Meperidine, prodrugs 62-67-9DP, Nalorphine, prodrugs 64-13-1DP, p-Methoxyamphetamine, prodrugs 76-41-5DP, Oxymorphone, prodrugs 76-42-6DP, Oxycodone, prodrugs 76-99-3DP, Methadone, prodrugs 77-07-6DP, Levorphanol, prodrugs 113-45-1DP, Methylphenidate, prodrugs 115-37-7DP, Thebaine, prodrugs 125-28-0DP, Dihydrocodeine, prodrugs 125-29-1DP, Hydrocodone, prodrugs 300-62-9DP, Amphetamine, prodrugs ***437-38-7DP***, Fentanyl, prodrugs 465-65-6DP, Naloxone, prodrugs 466-97-7DP, Normorphine, prodrugs 467-14-1DP, Neopine, prodrugs 469-62-5DP, Propoxyphene, prodrugs 537-46-2DP, Methamphetamine, prodrugs 561-27-3DP, Diacetylmorphine, prodrugs 1083-09-6DP, 2,4,5-Trimethoxyamphetamine, prodrugs 4764-17-4DP, 3,4-Methylenedioxyamphetamine, prodrugs 14357-76-7DP, Dihydroetorphine, prodrugs 14357-78-9DP, Diprenorphine, prodrugs 14521-96-1DP, Etorphine, prodrugs 15588-95-1DP, 2,5-Dimethoxy-4-methylamphetamine, prodrugs 16590-41-3DP, Naltrexone, prodrugs 20594-83-6DP, Nalbuphine, prodrugs 27203-92-5DP, Tramadol, prodrugs 40431-64-9DP, Methyl D-phenidate, prodrugs 42408-82-2DP, Butorphanol, prodrugs 43033-72-3DP, Levomethadyl acetate hydrochloride, prodrugs 51931-66-9DP, Tilidine, prodrugs 52485-79-7DP, Buprenorphine, prodrugs 55096-26-9DP, Nalmefene, prodrugs 56030-54-7DP, Sufentanil, prodrugs 59708-52-0DP, Carfentanil, prodrugs 61380-40-3DP, Lofentanil, prodrugs 68616-83-1DP, Penomorphone, prodrugs 71195-58-9DP, Alfentanil, prodrugs 73232-52-7DP, Methyl naltrexone, prodrugs 78995-14-9DP, β-Hydroxy-3-methylfentanyl, prodrugs 83387-25-1DP, N-Methylnaltrexone, prodrugs 132875-61-7DP, Remifentanil, prodrugs 926624-80-8P 926624-84-2P
(prodrugs of pharmacol. active agents)

IT ***437-38-7DP***, Fentanyl, prodrugs
(prodrugs of pharmacol. active agents)

RN 437-38-7 USPATFULL

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 51 OF 56 USPATFULL on STN

ACCESSION NUMBER:	2007:69247 USPATFULL Full-text
TITLE:	Pharmaceutical compositions for prevention of overdose or abuse
INVENTOR(S):	Mickle, Travis, Coralville, IA, UNITED STATES Krishnan, Suma, Belvedere, CA, UNITED STATES Moncrief, James Scott, Christiansburg, VA, UNITED STATES Lauderback, Christopher, Blacksburg, VA, UNITED STATES Miller, Christal, Coralville, IA, UNITED STATES Piccariello, Thomas, Blacksburg, VA, UNITED STATES
PATENT ASSIGNEE(S):	New River Pharmaceuticals Inc., Radford, VA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2007060500	A1	20070315		<--
APPLICATION INFO.:	US 2006-392878	A1	20060330	(11)	<--

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2004-US32131, filed on 30 Sep 2004, PENDING Continuation-in-part of Ser. No. US 2004-923088, filed on 23 Aug 2004, PENDING Continuation-in-part of Ser. No. US 2002-156527, filed on 29 May 2002, GRANTED, Pat. No. US 7060708 Continuation-in-part of Ser. No. US 2001-987458, filed on 14 Nov 2001, ABANDONED Continuation-in-part of Ser. No. US 2001-933708, filed on 22 Aug 2001, ABANDONED Continuation-in-part of Ser. No. US 2000-642820, filed on 22 Aug 2000, GRANTED, Pat. No. US 6716452 Continuation-in-part of Ser. No. US 2001-988071, filed on 16 Nov 2001, ABANDONED Continuation-in-part of Ser. No. US 2001-988034, filed on 16 Nov 2001, ABANDONED Continuation-in-part of Ser. No. WO 2001-US43089, filed on 14 Nov 2001, PENDING Continuation-in-part of Ser. No. WO 2001-US43117, filed on 16 Nov 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	WO 2001-US43117	20011116
	US	20001116
	US 2003-507012P	20030930 (60)
	US 2004-567800P	20040505 (60)
	US 2004-567802P	20040505 (60)
	US 2004-568011P	20040505 (60)
	US 2000-248748P	20001116 (60)
	US 2000-247594P	20001114 (60)
	US 2000-247684P	20001114 (60)
	US 2000-248733P	20001116 (60)
	US 2000-248528P	20001116 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HUNTON & WILLIAMS LLP, INTELLECTUAL PROPERTY DEPARTMENT, 1900 K STREET, N.W., SUITE 1200, WASHINGTON, DC, 20006-1109, US
NUMBER OF CLAIMS:	9
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	144 Drawing Page(s)
LINE COUNT:	3583

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to pharmaceutical compositions comprised of a chemical moiety attached to an active agent in a manner that substantially decreases the potential of the active agent to cause overdose or to be abused. When delivered at the proper dosage the pharmaceutical composition provides therapeutic activity similar to that of the parent active agent.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AI US 2006-392878 A1 20060330 (11) <--

DETD . . . and hydrocodone that are produced by modifying natural opium alkaloids and have similar chemical structures; and pure synthetics such as ***fentanyl*** and methadone that are not produced from opium and may have very different chemical structures than the opium alkaloids. Other. . .

DETD Exemplary narcotics include opioids, hydrocodone, oxycodone, morphine, dihydromorphine, ethylmorphine, codeine, hydromorphone, hydroxymorphone, oxymorphone, methyldihydromorphinone, methadone, ***fentanyl***, levorphanol, dihydrocodeine, meperidine, diphenoxylate, sufentanil, alfentanil, propoxyphene, pentazocine, nalbuphine, butorphanol, buprenorphine, meptazinol, naltrexone, dezocine or pharmaceutically acceptable salts thereof.

DETD . . . opioid prodrug. The active ingredients can be formulated into a single dosage form, or they can be formulated together or ***separately*** among multiple dosage forms. The active ingredients can be administered simultaneously or sequentially in any order.

DETD . . . emulsion, such as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The oils can be administered by adding the ***purified*** and sterilized liquids to a prepared enteral formula, which is then placed in the feeding tube of a patient who. . .

DETD . . . 5% H.sub.2SO.sub.4 in MeOH; R.sub.f(product)=.about.0.5). Reaction was neutralized to pH 7 with 6M HCl. Solvent was removed. Final product was ***purified*** using preparative TLC (0-10% MeOH in CHCl.sub.3). Solid was collected as a white powder (0.180 g, 41% yield): .sup.1H NMR. . .

DETD . . . up in CHCl.sub.3 (50 ml), washed with water (3+50 ml), dried over MgSO.sub.4, filtered and solvent removed. Final product was ***purified*** using preparative ***HPLC*** (10 mM CH.sub.3COONH.sub.4/MeCN; 0-20 min: 80/20→0/100). Solid was collected as a clear, colorless glass (0.095 g, 7% yield): .sup.1H NMR. . .

DETD . . . NMM followed by Boc-Ala-OSu. The solution was stirred at ambient temperatures for 18 hours. Solvent was removed. Crude material was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 100 water/0 0.1% TFA-MeCN→0/100; 30 ml/min.). Solid was collected as. . .

DETD . . . NMM followed by Boc-Gly-Gly-OSu. The solution was stirred at ambient temperatures for 18 hours. Solvent was removed. Crude material was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 90 water/10 0.1% TFA-MeCN→0/100; 30 ml/min.). Solid was collected as. . .

DETD . . . NMM followed by Boc-Gly-Gly-OSu. The solution was stirred at ambient temperatures for 18 hours. Solvent was removed. Crude material was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 85 water/15 0.1% TFA-MeCN→50/50; 30 ml/min.). Solid was collected as. . .

DETD . . . (3+150 ml), and brine (150 ml). The organic layer was dried over MgSO.sub.4, filtered, and solvent removed. Crude product was ***purified*** using recrystallization with IPAC/hexane solvent system. Final product was isolated as a white solid (1.025 g).

DETD . . . stirred for 30 minutes. The precipitate was filtered and washed thoroughly with water. Solid material was dried in vacuum and ***purified*** by ***reverse phase HPLC*** (2.77 g). Product was deprotected using 4N HCl in dioxane (.about.50 ml).

DETD . . . any excess phosgene. Solvent was then removed and product dried under vacuum for 18 hours. Product was used without further ***purification*** or characterization.

DETD . . . for 18 hours. Reaction was quenched by the addition of water, solvents were removed and crude product was isolated by ***purification*** with ***reverse-phase HPLC*** .

DETD Product was deprotected using 1:1 1M HCl: THF (1 ml/0.1 mmol) in 3 hours. Product was re-***purified*** by ***reverse-phase HPLC***.

DETD . . . NMM followed by Boc-(d)-Lys(Boc)-(1)-Lys(Boc)-OSu. The solution was stirred at ambient temperatures for 18 hours. Solvent was removed. Crude material was ***purified*** using preparative ***HPLC*** (Phenomenex Luna C18, 30+250 mm, 5 μM, 100 Å; Gradient: 90 water/10 0.1% TFA-MeCN→0/100; 30 ml/min.). Solid was collected as. . .

DETD . . . h. EtOAc part was washed with NaHCO3 and brine. Dried over Na.sub.2SO.sub.4 and evaporated to dryness. Compound was obtained by ***purification*** over silica gel column (30% EtOAc/Hexane).

DETD . . . 1 h. The EtOAc portion was washed with water, brine, dried over Na.sub.2SO.sub.4 and evaporated to dryness. The residue was ***purified*** over silica gel (70% EtOAc-Hexane) to give the title compound.

DETD . . . taken in EtOAc (50 mL), washed with satd. NaHCO.sub.3, brine, dried over Na.sub.2SO.sub.4 and evaporated to dryness. The residue was ***purified*** over silila gel to give the title compound.

DETD . . . The EtOAc part was washed with water, aq. NaHCO.sub.3, brine, dried over Na.sub.2SO.sub.4 and evaporated to dryness. The residue was ***purified*** over silica gel to give the title compound.

DETD . . . 1 h. The organic part was washed with water, brine, dried over Na.sub.2SO.sub.4 and evaporated to dryness. The residue was ***purified*** over silica gel to give the title compound.

DETD . . . 1 h. The organic part was washed with water, brine, dried over Na.sub.2SO.sub.4 and evaporated to dryness. The residue was ***purified*** over silica gel to give the title compound.

DETD . . . The reaction was stirred at ambient temperatures for 18 hours, quenched with water and solvents removed. Crude protected product was ***purified*** using ***reverse-phase HPLC***. Deprotection occurred with 4N HCl in dioxane (20 ml/mmol) to obtain Phe-Oxycodone.

DETD . . . The reaction was stirred at ambient temperatures for 18 hours, quenched with water, and solvents removed. Crude protected product was ***purified*** using ***reverse phase HPLC***. Deprotection occurred using 4N HCl in dioxane (20 ml/mmol) to obtain Pro.sub.2-Leu-Oxycodone.

DETD . . . 1 h. EtOAc part was washed with NaHCO.sub.3 and brine. Dried over Na.sub.2SO.sub.4 and evaporated to dryness. Crude product was ***purified*** with either silica gel column. (30% EtOAc/Hexane).

DETD . . . followed by Boc-XX.sub.2--OSu (4.1). Reaction was stirred at ambient temperature for 24 hours. Solvents were removed and crude product was ***purified*** by ***reverse phase HPLC***.

DETD . . . by Boc-(1)-Lys(Boc)-(d)-Lys(Boc)-OSu (3 eq). Reaction was stirred at ambient temperature for 24 hours. Solvents were removed and crude product was ***purified*** by ***reverse phase***

HPLC.

DETD . . . 1 h. EtOAc part was washed with NaHCO.sub.3 and brine. Dried over Na.sub.2SO.sub.4 and evaporated to dryness. Crude product was ***purified*** with either silica gel column. (30% EtOAc/Hexane).

DETD . . . 1 h. EtOAc part was washed with NaHCO.sub.3 and brine. Dried over Na.sub.2SO.sub.4 and evaporated to dryness. Crude product was ***purified*** with either silica gel column. (30% EtOAc/Hexane).

DETD . . . water (3+100 ml). The organic layer was dried over MgSO.sub.4 and solvents were removed under reduced pressure. Crude product was ***purified*** over silica gel (0-10% MeOH in CHCl.sub.3) to obtain the ketal conjugate (0.010 g) in a 1:1 mixture with free. . .

DETD . . . (1.0M in THF, 5.92 mmol) dropwise via syringe. This solution was stirred at -78° C. for 1 hour. In a ***separate*** reaction, Boc-Ser-OtBu (0.220 g, 0.84 mmol) was dissolved in THF (5 ml) with NMM (0.10 ml, 0.92 mmol) and triphosgene. . .

DETD Polyserine-naltrexone conjugates were tested in male Sprague Dawley rats (.about.250 g). Defined doses were delivered orally in gelatin capsules containing ***purified*** dry powder polyserine-naltrexone conjugates or naltrexone. No excipients were added to the capsules. Content of naltrexone in the PolySerine-Naltrexone conjugate. . .

DETD Polyserine-naltrexone conjugates were tested in Sprague-dawley rats (.about.250 g). Defined doses were delivered orally in gelatin capsules containing ***purified*** dry powder polyserine-naltrexone conjugates or naltrexone. No excipients were added to the capsules. Content of naltrexone in the polyserine-naltrexone conjugate. . .

DETD . . . was removed from the monlayers and concentrated on SP-18 columns. Concentrated samples were analyzed for the presence of naltrexone by ***reverse phase HPLC***. Each Polyserine-naltrexone conjugate showed significant release of free naltrexone from the polymer conjugate in three ***separate*** samples. In conclusion, Caco-2 cellular enzymes affected release of naltrexone from Polyserine-naltrexone conjugates BB-272 and BB-301. Release of carbonate linked. . .

L112 ANSWER 52 OF 56 USPATFULL on STN

ACCESSION NUMBER:	2005:234176 USPATFULL Full-text				
TITLE:	Narcotic-NSAID ion pairs				
INVENTOR(S):	Sancilio, Frederick D., Jupiter, FL, UNITED STATES Stowell, Grayson W., Wilmington, NC, UNITED STATES Whittall, Linda B., Wilmington, NC, UNITED STATES White, David, Wilmington, NC, UNITED STATES Whittle, Robert R., Wilmington, NC, UNITED STATES				
	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2005203115	A1	20050915		<--
APPLICATION INFO.:	US 2004-796308	A1	20040310	(10)	<--
DOCUMENT TYPE:	Utility				
FILE SEGMENT:	APPLICATION				
LEGAL REPRESENTATIVE:	FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007, US				
NUMBER OF CLAIMS:	160				
EXEMPLARY CLAIM:	1				
NUMBER OF DRAWINGS:	1 Drawing Page(s)				
LINE COUNT:	4919				

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an ion pair compound of the formula [narcotic].sup.+[A].sup.-, wherein [narcotic].sup.+ represents at least one cation of at least one narcotic agent or one or more stereochemical isomers

thereof and [A].sup.- represents at least one anion of at least one NSAID or one or more stereochemical isomers thereof. An example of the ion pair compound is propoxyphene diclofenate. The ion pair compounds, or their pharmaceutical compositions, are useful in methods of treating a wide variety of conditions that indicate analgesics, anti-inflammatory agents, or both. Under the conditions prescribed for their use, the ion pair compounds exhibit poor or complete insolubility but excellent chemical stability in low pH environments, such as those found in the stomach. The ion pair compounds readily dissolve and dissociate in higher pH environments such as the small intestine to release the constituent narcotic and NSAID.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AI US 2004-796308 A1 20040310 (10) <--

DETD Preferred narcotics in this regard include but are not limited to ketamine, oxycodone, propoxyphene, methadone, hydrocodone, morphine, codeine, ***fentanyl***, meperidine, hydromorphone, oxymorphone, dihydrocodeine, nalbuphine, and buprenorphine. More preferred are meperidine, ketamine, oxycodone, propoxyphene, methadone, hydrocodone, morphine, and codeine. Even. . .

DETD . . . oxycodone etodolate, oxycodone sulindate, oxycodone ketoprofenate, oxycodone suprofenate, oxycodone flurbiprofenate, oxycodone tolmetinate, oxycodone fenoprofenate, oxycodone oxaprozinate, oxycodone difunisalate, oxycodone loxoprofenate; ***fentanyl*** naproxenate, ***fentanyl*** etodolate, ***fentanyl*** ketoprofenate, ***fentanyl*** sulindate, ***fentanyl*** suprofenate, ***fentanyl*** flurbiprofenate, ***fentanyl*** tolmetinate, ***fentanyl*** fenoprofenate, ***fentanyl*** oxaprozinate, ***fentanyl*** difunisalate, ***fentanyl*** loxoprofenate, meperidine naproxenate, meperidine etodolate, meperidine ketoprofenate, meperidine sulindate, meperidine suprofenate, meperidine flurbiprofenate, meperidine tolmetinate, meperidine fenoprofenate, meperidine oxaprozinate, meperidine. . .

DETD Another solubilizing agent which may be utilized in compositions of the present invention is water, especially ***purified***, and most preferably, deionized. For such compositions, the concentration of water is from about zero percent to about ninety-nine percent. . .

DETD . . . yield the present ion pair compound. In one embodiment, the compounds of formulae {[narcotic].sup.+}.sub.xX.sup.x- and [A].sup.-[B].sup.+ thus are dissolved in ***separate*** volumes of the same solvent or in different solvents. When combined, the resultant solution thus yields the ion pair compound. . . X.sup.x- and B.sup.+. The solvent or solvent mixture can be selected such that the ion pair compound precipitates when the ***separate*** volumes of {[narcotic].sup.+}.sub.xX.sup.x- and [A].sup.-[B].sup.+ are combined, thereby allowing the easy isolation of the ion pair compound. Alternatively, the ion. . . different solvents. In this scenario, the solvent(s) may be removed to yield the ion pair compound, which can then be ***purified*** according to standard ***purification*** techniques known to those who are skilled in the art.

DETD . . . dissolved in a solution of methanol and water (5:1) resulting in the formation of a white precipitate. The precipitate was ***separated*** by filtration through Whatman #4 filter paper and dried under nitrogen. The product was characterized by FTIR spectroscopy. Representative bands. . .

DETD . . . Representative bands are listed in Table 3. The residual solid was dissolved in toluene (80 mL) and transferred to a ***separatory*** funnel. The organic layer was washed with water (3+40 mL), dried (MgSO.sub.4), and the resulting solid ***separated*** by filtration through a 0.45-μm polyvinylidene fluoride (PVDF) filter. The solvent

was removed by rotary evaporation, which resulted in an. . .

DETD . . . a white precipitate. After mixing for 15 minutes, the contents of the 1 L Erlenmeyer flask were transferred to a ***separatory*** funnel with the aid of a small portion of diethyl ether. Diethyl ether (250 mL) was added to the ***separatory*** funnel and any remaining precipitate was dissolved with shaking. The organic and aqueous layers were ***separated*** and the aqueous layer washed with additional diethyl ether (2+250 mL) to extract any remaining product. The organic layers were. . .

DETD . . . precipitate. Upon addition of the diethyl ether, the precipitate dissolved with stirring. The resulting aqueous/organic solution was transferred to a ***separatory*** funnel in several portions and the organic and aqueous layers ***separated***. The organic layers were combined, the diethyl ether removed by rotary evaporation and the product placed under vacuum. The resulting. . .

DETD . . . precipitate. Upon addition of the diethyl ether, the precipitate dissolved with stirring. The resulting aqueous/organic solution was transferred to a ***separatory*** funnel in several portions and the organic and aqueous layers ***separated***. The organic layers were combined, the diethyl ether removed by rotary evaporation and the product placed under vacuum. The resulting. . .

DETD . . . 250 mL Erlenmeyer flask. A white precipitate formed and the solution was stirred for 15 minutes. The solid material was ***separated*** by filtration through a 0.45-μm polyvinylidene fluoride (PVDF) filter and the filter cake dissolved in methanol (25 mL). The methanol. . .

DETD . . . After an attempt to remove the precipitate by filtration was unsuccessful, the aqueous solution and precipitate were transferred to a ***separatory*** funnel using a small portion of diethyl ether to aid in the transfer. Additional diethyl ether was added to the ***separatory*** funnel (250 mL) and any remaining precipitate was dissolved with shaking. After ***separation*** of the organic and aqueous layers, the aqueous solution was washed with additional diethyl ether (2+250 mL) to extract any. . .

DETD . . . the solution was stirred for 30 minutes. The contents of the 250 mL round bottom flask were transferred to a ***separatory*** funnel using a small portion of diethyl ether to aid in the transfer. Diethyl ether (90 mL) and chloroform (90 mL) were added to the ***separatory*** funnel and any remaining precipitate was dissolved with shaking. The organic layer was ***separated*** and the solvent removed by rotary evaporation. The resulting white solid was dissolved in diethyl ether (100 mL) and the. . .

DETD . . . drops of acetone. Water was added until a precipitate formed and the contents of the test tube transferred to a ***separatory*** funnel containing diethyl ether (8 mL). The solid product was dissolved in the diethyl ether, and then was extracted and the organic layer ***separated*** and set aside to evaporate. Upon evaporation of the diethyl ether, the resulting product was characterized by single crystal X-ray. . .

DETD . . . propoxyphene solution forming a white precipitate. After mixing for 2 hours, the contents of the beaker were transferred to a ***separatory*** funnel with the aid of a small portion of diethyl ether. Additional diethyl ether was added to the ***separatory*** funnel (100 mL) and any remaining precipitate dissolved with shaking. The aqueous and organic layers were ***separated*** and the aqueous layer was washed with an additional portion of diethyl ether (100 mL) to extract any remaining product. The organic and aqueous layers were ***separated*** again, the organic layers combined, washed with water (50 mL), and the solvent removed by rotary evaporation. The resulting oily. . .

DETD . . . forming a white precipitate. After mixing for 1.5 hours, the contents of the 500 mL beaker were transferred to a ***separatory*** funnel with the aid of a small portion of diethyl ether. Additional diethyl ether was added to the ***separatory*** funnel (125 mL) and any remaining precipitate was dissolved with shaking. The aqueous and organic layers were ***separated*** and the aqueous layer washed with additional portions of diethyl ether (2+125 mL) to extract any remaining product. The organic. . .

DETD . . . oxycodone solution forming a white precipitate. After mixing for 1 hour, the aqueous solution and precipitate were transferred to a ***separatory*** funnel and diethyl ether was added (20 mL). Diethyl ether (20 mL) was also added to the 100 mL round bottom flask to dissolve any remaining precipitate. This solution was added to the ***separatory*** funnel, and any precipitate in the ***separatory*** funnel was dissolved with shaking. the organic layer ***separated*** and the solvent removed by rotary evaporation. The resulting oily material was placed under reduced pressure to form a white. . .

DETD . . . After reduction, a white precipitate was observed. The contents of the 500 mL round bottom flask were transferred to a ***separatory*** funnel with the aid of a small amount of diethyl ether. Additional diethyl ether (90 mL) was added to the ***separatory*** funnel and any remaining precipitate was dissolved with shaking. The aqueous and organic layers were ***separated*** and the aqueous layer was washed with additional diethyl ether (3+90 mL) to extract any remaining product. The organic layers. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . solution. The solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . 1.00 mmol) are combined into an suitable flask and stirred for 60 minutes. The resulting solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent

removed. . .

DETD . . . 1.00 mmol) are combined into an suitable flask and stirred for 60 minutes. The resulting solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . The resulting solution is stirred and the total volume reduced to approximately 30 mL. The solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . 1.00 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

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DETD . . . 0.50 mmol) are combined into a suitable flask and stirred for 60 minutes. The resulting solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

DETD . . . resulting solution is stirred and the total volume reduced to approximately 30 mL. The concentrated solution is transferred to a ***separatory*** funnel and the desired product extracted with diethyl ether (4+90 mL). The organic layers are combined and the solvent removed. . .

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DETD . . . at about 50° C. A thick sticky white precipitate formed as the mixture was stirred. The reaction was monitored by ***HPLC*** to calculate the amount of propoxyphene remaining in solution. When the reaction was considered complete, as evidence by the disappearance. . . and the solid product washed with multiple aliquots of water (about 2000 mL) at 50° C. with mechanical stirring until ***HPLC*** confirmed only low levels of unreacted sodium diclofenac present. The solid material was then dissolved in a minimal amount of. . .

DETD . . . about 50° C. A thick sticky white precipitate formed as the solution was stirred. Completeness of reaction was confirmed by ***HPLC*** to determine the amount of unreacted propoxyphene hydrochloride remaining in solution (about 1 mg/mL remained). The reaction was considered complete,. . . washed with numerous aliquots of water (about 300 mL for each washing) at about 50° C. with mechanical stirring until ***HPLC*** confirmed only low levels of unreacted sodium diclofenate remained (about 0.2 mg/mL). The solid material was then dissolved in a. . .

DETD . . . A thick sticky white precipitate formed as the solution was stirred over several hours. Completeness of reaction was confirmed by ***HPLC*** to determine the amount of unreacted propoxyphene hydrochloride remaining in solution (about 1 mg/mL remained). The reaction was considered complete. . . washed with numerous aliquots of water (about 500 mL for each washing) at about 50° C. with mechanical stirring until ***HPLC*** confirmed only low levels of unreacted sodium diclofenate remained (about 0.2 mg/mL). The solid material was then dissolved in a. . .

DETD Analysis of Washings of Propoxyphene Diclofenate Synthesis Using High Pressure ***Liquid Chromatography*** (***HPLC***)

DETD . . . remove excess diclofenac (sodium or potassium). The levels of diclofenac salts were monitored to determine the reaction end point by

HPLC according to the following procedure.

DETD ***HPLC*** was performed with the HP1100 system (Hewlett Packard, Palo Alto, Calif.). The method utilized a 4.6+150 mm C.sub.18 column (Waters. . .

DETD Analysis of the Aqueous Mother Liquor and Subsequent Washings During Propoxyphene Diclofenate Synthesis Using High Pressure ***Liquid Chromatography***

DETD . . . examples the reaction was considered complete once the reaction mixture contained an acceptably low level of propoxyphene as determined by ***HPLC***. When the reaction was complete, the aqueous mother liquor was decanted and the product washed with numerous aqueous rinses to remove excess diclofenac (sodium or potassium). Using an ***HPLC*** analysis according to the following procedure, the propoxyphene and diclofenac levels were monitored during the reaction to determine the end. . .

DETD For each of the procedures above, ***HPLC*** was performed with the HP 1100 system (Hewlett Packard, Palo Alto, Calif.). The method utilized a 4.6+150 mm C.sub.18 column. . .

CLM What is claimed is:

. . . 1, wherein the narcotic in [narcotic].sup.+ is selected from the group consisting of ketamine, oxycodone, propoxyphene, methadone, hydrocodone, morphine, codeine, ***fentanyl***, meperidine, hydromorphone, oxymorphone, dihydrocodeine, nalbuphine, and buprenorphine.

. . . oxycodone etodolate, oxycodone sulindate, oxycodone ketoprofenate, oxycodone suprofenate, oxycodone flurbiprofenate, oxycodone tolmetinate, oxycodone fenoprofenate, oxycodone oxaprozinate, oxycodone difunisalate, oxycodone loxoprofenate, ***fentanyl*** naproxenate, ***fentanyl*** etodolate, ***fentanyl*** ketoprofenate, ***fentanyl*** sulindate, ***fentanyl*** suprofenate, ***fentanyl*** flurbiprofenate, ***fentanyl*** tolmetinate, ***fentanyl*** fenoprofenate, ***fentanyl*** oxaprozinate, ***fentanyl*** difinisalate, ***fentanyl*** loxoprofenate, meperidine naproxenate, meperidine etodolate, meperidine ketoprofenate, meperidine sulindate, meperidine suprofenate, meperidine flurbiprofenate, meperidine tolmetinate, meperidine fenoprofenate, meperidine oxaprozinate, meperidine. . .

. . . oxycodone etodolate, oxycodone sulindate, oxycodone ketoprofenate, oxycodone suprofenate, oxycodone flurbiprofenate, oxycodone tolmetinate, oxycodone fenoprofenate, oxycodone oxaprozinate, oxycodone difunisalate, oxycodone loxoprofenate, ***fentanyl*** naproxenate, ***fentanyl*** etodolate, ***fentanyl*** ketoprofenate, ***fentanyl*** sulindate, ***fentanyl*** suprofenate, ***fentanyl*** flurbiprofenate, ***fentanyl*** tolmetinate, ***fentanyl*** fenoprofenate, ***fentanyl*** oxaprozinate, ***fentanyl*** difunisalate, ***fentanyl*** loxoprofenate, meperidine naproxenate, meperidine etodolate, meperidine ketoprofenate, meperidine sulindate, meperidine suprofenate, meperidine flurbiprofenate, meperidine tolmetinate, meperidine fenoprofenate, meperidine oxaprozinate, meperidine. . .

. . . oxycodone etodolate, oxycodone sulindate, oxycodone ketoprofenate, oxycodone suprofenate, oxycodone flurbiprofenate, oxycodone tolmetinate, oxycodone fenoprofenate, oxycodone oxaprozinate, oxycodone difunisalate, oxycodone loxoprofenate ***fentanyl*** naproxenate, ***fentanyl*** etodolate, ***fentanyl*** ketoprofenate, ***fentanyl*** sulindate, ***fentanyl*** suprofenate, ***fentanyl*** flurbiprofenate, ***fentanyl*** tolmetinate, ***fentanyl*** fenoprofenate, ***fentanyl*** oxaprozinate, ***fentanyl*** difunisalate, ***fentanyl*** loxoprofenate,

meperidine naproxenate, meperidine etodolate, meperidine ketoprofenate, meperidine sulindate, meperidine suprofenate, meperidine flurbiprofenate, meperidine tolmetinate, meperidine fenoprofenate, meperidine oxaprozinate, meperidine. . .

. . . oxycodone etodolate, oxycodone sulindate, oxycodone ketoprofenate, oxycodone suprofenate, oxycodone flurbiprofenate, oxycodone tolmetinate, oxycodone fenoprofenate, oxycodone oxaprozinate, oxycodone difunisalate, oxycodone loxoprofenate ***fentanyl*** naproxenate, ***fentanyl*** etodolate, ***fentanyl*** ketoprofenate, ***fentanyl*** sulindate, ***fentanyl*** suprofenate, ***fentanyl*** flurbiprofenate, ***fentanyl*** tolmetinate, ***fentanyl*** fenoprofenate, ***fentanyl*** oxaprozinate, ***fentanyl*** difunisalate, ***fentanyl*** loxoprofenate, meperidine naproxenate, meperidine etodolate, meperidine ketoprofenate, meperidine sulindate, meperidine suprofenate, meperidine flurbiprofenate, meperidine tolmetinate, meperidine fenoprofenate, meperidine oxaprozinate, meperidine. . .

. . . oxycodone etodolate, oxycodone sulindate, oxycodone ketoprofenate, oxycodone suprofenate, oxycodone flurbiprofenate, oxycodone tolmetinate, oxycodone fenoprofenate, oxycodone oxaprozinate, oxycodone difunisalate, oxycodone loxoprofenate ***fentanyl*** naproxenate, ***fentanyl*** etodolate, ***fentanyl*** ketoprofenate, ***fentanyl*** sulindate, ***fentanyl*** suprofenate, ***fentanyl*** flurbiprofenate, ***fentanyl*** tolmetinate, ***fentanyl*** fenoprofenate, ***fentanyl*** oxaprozinate, ***fentanyl*** difunisalate, ***fentanyl*** loxoprofenate, meperidine naproxenate, meperidine etodolate, meperidine ketoprofenate, meperidine sulindate, meperidine suprofenate, meperidine flurbiprofenate, meperidine tolmetinate, meperidine fenoprofenate, meperidine oxaprozinate, meperidine. . .

153. The process according to claim 152, further comprising dissolving {[narcotic].sup.+}.sub.xX.sup.-x and [A].sup.-B.sup.+ in ***separate*** volumes of the same solvent or different solvents prior to the contacting.

IT 6020-73-1P 28684-49-3P 66424-55-3P 66424-56-4P 140898-60-8P
195140-65-9P 864494-95-1P 864494-96-2P 864494-97-3P 864494-98-4P
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864495-04-5P 864495-05-6P 864495-06-7P 864495-07-8P 864495-09-0P
864495-10-3P 864495-11-4P 864495-12-5P 864495-13-6P 864495-14-7P
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864495-30-7P 864495-31-8P 864495-32-9P 864495-33-0P 864495-34-1P
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864495-61-4P 864495-62-5P 864495-63-6P 864495-64-7P 864495-65-8P
864495-66-9P 864495-67-0P 864495-68-1P 864495-69-2P 864495-70-5P
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864495-81-8P 864495-82-9P 864495-83-0P 864495-84-1P 864495-85-2P
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864496-11-7P 864496-12-8P 864496-13-9P 864496-14-0P 864496-15-1P

864496-16-2P 864496-17-3P 864496-18-4P 864496-19-5P 864496-20-8P
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864496-33-3P 864496-34-4P 864496-35-5P
864496-36-6P 864496-37-7P 864496-38-8P
864496-39-9P 864496-40-2P 864496-41-3P
864496-42-4P 864496-43-5P 864496-44-6P 864496-45-7P
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864496-61-7P 864496-62-8P 864496-63-9P 864496-64-0P 864496-65-1P
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864517-46-4P 864517-48-6P 864517-49-7P
(preparation of narcotic-NSAID ion pairs)

IT ***864496-33-3P 864496-34-4P 864496-35-5P***
864496-36-6P 864496-37-7P 864496-38-8P
864496-39-9P 864496-40-2P 864496-41-3P
864496-42-4P 864496-43-5P
(preparation of narcotic-NSAID ion pairs)

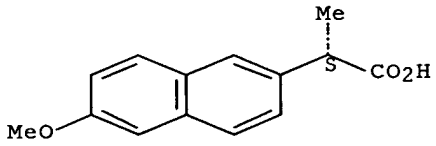
RN 864496-33-3 USPATFULL

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (αS)-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

CM 1

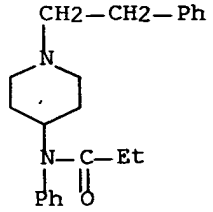
CRN 22204-53-1
CMF C14 H14 O3

Absolute stereochemistry. Rotation (+).



CM 2

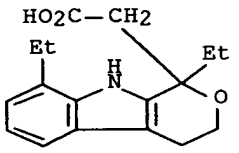
CRN 437-38-7
CMF C22 H28 N2 O



RN 864496-34-4 USPATFULL
CN Pyrano[3,4-b]indole-1-acetic acid, 1,8-diethyl-1,3,4,9-tetrahydro-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

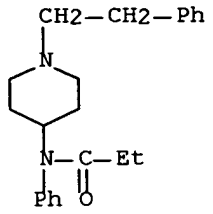
CM 1

CRN 41340-25-4
CMF C17 H21 N O3



CM 2

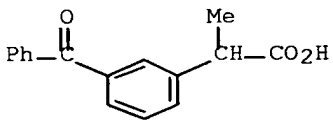
CRN 437-38-7
CMF C22 H28 N2 O



RN 864496-35-5 USPATFULL
CN Benzeneacetic acid, 3-benzoyl-α-methyl-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

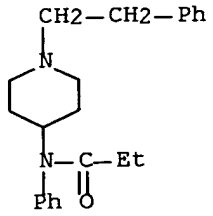
CM 1

CRN 22071-15-4
CMF C16 H14 O3



CM 2

CRN 437-38-7
CMF C22 H28 N2 O

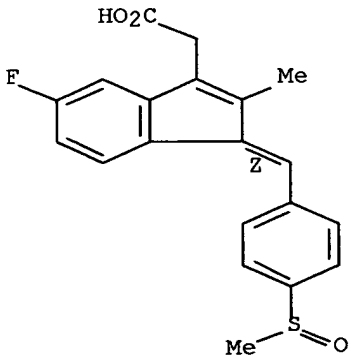


RN 864496-36-6 USPATFULL
CN 1H-Indene-3-acetic acid, 5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl]methylene]-, (1Z)-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

CM 1

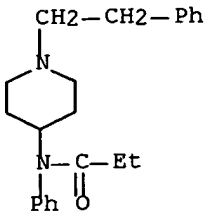
CRN 38194-50-2
CMF C20 H17 F O3 S
CDES 2:Z

Double bond geometry as shown.



CM 2

CRN 437-38-7
CMF C22 H28 N2 O

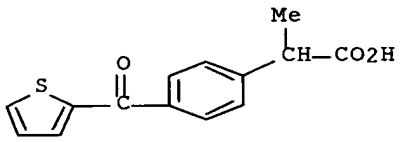


RN 864496-37-7 USPATFULL

CN Benzeneacetic acid, α-methyl-4-(2-thienylcarbonyl)-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

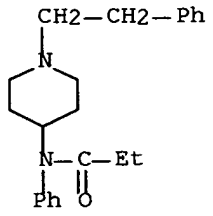
CM 1

CRN 40828-46-4
CMF C14 H12 O3 S



CM 2

CRN 437-38-7
CMF C22 H28 N2 O

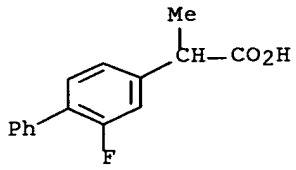


RN 864496-38-8 USPATFULL

CN [1,1'-Biphenyl]-4-acetic acid, 2-fluoro-α-methyl-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

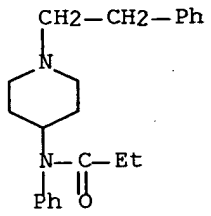
CM 1

CRN 5104-49-4
CMF C15 H13 F O2



CM 2

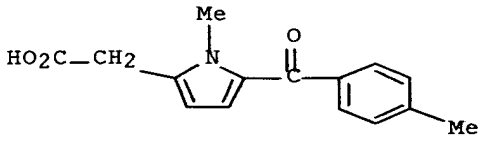
CRN 437-38-7
CMF C22 H28 N2 O



RN 864496-39-9 USPATFULL
CN 1H-Pyrrole-2-acetic acid, 1-methyl-5-(4-methylbenzoyl)-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

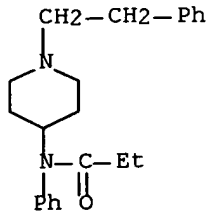
CM 1

CRN 26171-23-3
CMF C15 H15 N O3



CM 2

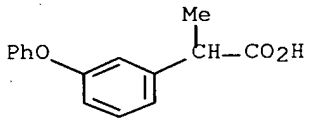
CRN 437-38-7
CMF C22 H28 N2 O



RN 864496-40-2 USPATFULL
CN Benzeneacetic acid, α-methyl-3-phenoxy-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

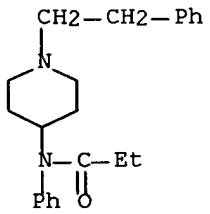
CM 1

CRN 29679-58-1
CMF C15 H14 O3



CM 2

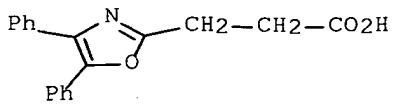
CRN 437-38-7
CMF C22 H28 N2 O



RN 864496-41-3 USPATFULL
CN 2-Oxazolepropanoic acid, 4,5-diphenyl-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

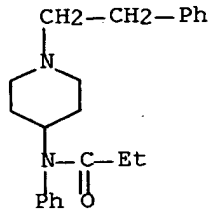
CM 1

CRN 21256-18-8
CMF C18 H15 N O3



CM 2

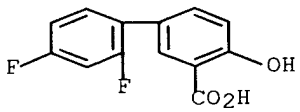
CRN 437-38-7
CMF C22 H28 N2 O



RN 864496-42-4 USPATFULL
CN [1,1'-Biphenyl]-3-carboxylic acid, 2',4'-difluoro-4-hydroxy-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

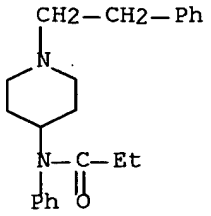
CM 1

CRN 22494-42-4
CMF C13 H8 F2 O3



CM 2

CRN 437-38-7
CMF C22 H28 N2 O

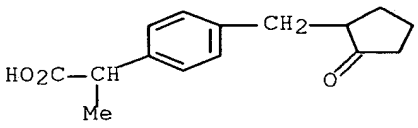


RN 864496-43-5 USPATFULL

CN Benzeneacetic acid, α-methyl-4-[(2-oxocyclopentyl)methyl]-, compd. with N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (1:1) (CA INDEX NAME)

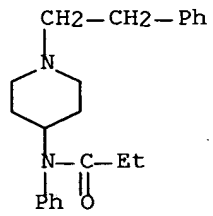
CM 1

CRN 68767-14-6
CMF C15 H18 O3



CM 2

CRN 437-38-7
CMF C22 H28 N2 O



L112 ANSWER 53 OF 56 USPATFULL on STN

ACCESSION . . .

chemical group that can then undergo a second reaction to release the drug. In a preferred embodiment, the narcotic analgesic ***fentanyl*** covalently attached to an inert polymer by way of its nitrogen through the formation of a quaternary vinylammonium salt, and. . .

AI US 2004-859472 A1 20040601 (10) <--

AB . . . chemical group that can then undergo a second reaction to release the drug. In a preferred embodiment, the narcotic analgesic ***fentanyl***

covalently attached to an inert polymer by way of its nitrogen through the formation of a quaternary vinylammonium salt, and. . .

SUMM . . . can then undergo a second reaction to release the drug. In a particular embodiment of this invention, the narcotic analgesic ***fentanyl*** is covalently attached to an inert polymer by way of its nitrogen through the formation of a quaternary vinylammonium salt,. . . . the nucleophilic atom involved in the intramolecular substitution reaction. Thus, in another particular embodiment of this invention, the narcotic analgesic ***fentanyl*** is covalently attached to an inert polymer by way of its nitrogen through the formation of a quaternary vinylammonium salt,. . .

DETD . . . bonded to the remainder of the drug-delivery molecule. Preferred drugs include drugs incorporating tertiary amines: narcotic analgesic drugs, including oxycodone, ***fentanyl***, and propoxyphene; and mechlorethamine (an anti-neoplastic); drugs incorporating secondary amines, including methyl phenidate (Ritalin) (a central nervous system stimulant, and. . .

DETD [0038] As used herein a spacer is a series of atoms in a chain ***separating*** the triggering atom and the carbon to which the drug is attached. Preferably the spacer is Qn as defined herein,. . .

DETD . . . a faster rate is desired and less easily hydrolyzed when a slower rate is desired. The unmasking reactions can be ***separately*** controlled to occur under different conditions, if desired.

DETD [0131] Specific drugs useful in this invention include narcotic analgesic drugs such as oxycodone, ***fentanyl***, and propoxyphene; mechlorethamine (an anti-neoplastic); drugs incorporating secondary amines, including methyl phenidate (Ritalin) (a central nervous system stimulant, and bis-(2-chloroethyl)amine. . .

DETD [0140] Two specific nucleophilic vinylic substitution drug-delivery molecules for ***fentanyl*** have at least some repeating units having the following structures: ##STR7##

DETD . . . drug. The combination of drug delivery compositions may be done either at a crude physical level by mixing together the ***separately***-prepared drug-delivery polymers, or may be done at a molecular level by using polymers that have a mixture of drug delivery. . .

DETD . . . possible fashion to achieve reaction of the more reactive of the two functional groups. Since it is not possible to ***purify*** a polymer-supported molecule, control of the amount of reagent employed in such reactions requiring discrimination between functional groups relies on. . .

DETD [0315] Laboratory scale ***separation*** of the polymer-supported molecules from excess reagent is carried out by transferring the polymer and any solution to one or. . .

DETD [0316] Scheme 8 shows preparation and operation of a drug delivery composition that utilizes a masked oxygen triggering atom, using ***fentanyl*** as the example drug.

DETD Formation of an Vinylically-bound ***Fentanyl*** Delivery Composition having an Acetal Masked Oxygen Triggering Atom

DETD [0318] The precursor resin prepared above (tosylate or triflate) is treated with a saturated solution of ***fentanyl*** in chloroform and heated at about 40° with swirling for a sufficient time to allow formation of the vinylammonium salt of oxycodone. When reaction is complete, the ***Fentanyl*** Drug Delivery Composition is centrifuged and the solid washed to recover unreacted ***fentanyl*** , which may be recycled. Those familiar with the art recognize that different drugs may require somewhat different conditions to accomplish. . .

DETD . . . minutes, the solution is heated at reflux for 18 hours. After

removal of solvent by rotary evaporation, the Boc-derivative is ***separated*** from residual 4-amino-3-bromophenol by chromatography on silica gel. A portion of the 4-tert-butoxycarbonylamido-3-bromophenol so obtained (23 g) is dissolved in. . . an estimate of the yield. The polymeric propargyl alcohol is combined with dichloromethane and four molar equivalents of 2,6-di-tert-butylpyridine. Freshly ***purified*** Dess-Martin periodinane reagent (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, 1.5 molar equivalents) is added and the mixture swirled for four hours at room temperature. The. . .

DETD Preparation of a Polymeric Vinylically-bound ***Fentanyl*** Delivery Composition having an Amine Nucleophilic Triggering Atom

DETD [0320] This preparation is illustrated in Scheme 10. A saturated methanol solution of the tetrafluoroborate salt of ***fentanyl*** is combined with the polymeric precursor for the drug delivery composition incorporating a carbamate masked nitrogen triggering atom, along with sufficient methanol to cover the polymer, and the mixture heated at reflux until the reaction is complete. Excess ***fentanyl*** is recovered by centrifugation or filtration, and the resin is washed with methanol to complete this recovery. Those familiar with. . .

DETD [0322] The polymeric ***fentanyl*** drug delivery composition may be encapsulated or put into tabular form. If chewed in the mouth, no ***fentanyl*** will be released, since quaternary vinylammonium salts are quite stable in neutral aqueous solution, and the masking ethoxyethyl group (or. . . unmask the triggering group, which will then engage in an intramolecular nucleophilic substitution reaction by an addition-elimination sequence to release ***fentanyl*** in its physiologically active form.

DETD . . . The amount of unreacted oxycodone is monitored over time by periodic removal of aliquots and assay by an appropriate technique (***HPLC*** is convenient). for the presence of oxycodone; if all of the oxycodone disappears, additional portions of oxycodone saturated chloroform are. . .

CLM What is claimed is:

48. The drug-delivery molecule of claim 38 for release of ***fentanyl*** selected from the group consisting of drug molecule moieties of the formulas: ##STR56## wherein n is 0-2; and ##STR57## wherein. . .

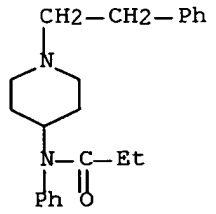
. . . a drug selected from the group consisting of amine, alcohol or thiol drugs selected from the group consisting of oxycodone; ***fentanyl*** ; propoxyphene; mechlorethamine; methyl phenidate (Ritalin); bis-(2-chloroethyl)amine; isosorbide mononitrate; fluvastatin; lovastatin; codeine; acetamidophenol; mensa sodium (2-mercaptoethanesulfonic acid, sodium salt); captropril; daunorubicin;. . .

IT 76-42-6DP, Oxycodone, reaction products with polymer derivs. 109-92-2DP, reaction products with polymer derivs. and drugs 125-29-1DP, Hydrocodone, reaction products with polymer derivs. 126-30-7DP, reaction products with polymer derivs. and drugs ***437-38-7DP***, Fentanyl, reaction products with polymer derivs. 542-28-9DP, reaction products with polymer derivs. and drugs 619-45-4DP, reaction products with polymer derivs. and drugs 624-67-9DP, 2-Propynal, reaction products with polymer derivs. and drugs 870-46-2DP, reaction products with poly(aspartic acid) 929-06-6DP, reaction products with polymer derivs. and drugs 9002-88-4DP, Polyethylene, derivs., reaction products with drugs 9003-17-2DP, Polybutadiene, derivs., reaction products with drugs 9003-53-6DP, Polystyrene, derivs., reaction products with drugs 9004-67-5DP, Methyl cellulose, derivs., reaction products with drugs 9046-31-5DP, Poly(vinylbenzoic acid), derivs., reaction products with drugs 9080-67-5DP, Poly(vinylbenzyl chloride), derivs., reaction products with

drugs 24424-99-5DP, reaction products with polymer derivs. and drugs 24936-50-3DP, Poly(4-bromostyrene), derivs., reaction products with fentanyl 25608-40-6DP, Poly(aspartic acid), reaction products with amines 26009-03-0DP, Poly(glycolic acid), derivs., reaction products with drugs 26023-30-3DP, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)], derivs., reaction products with drugs 26063-13-8DP, Poly(aspartic acid), reaction products with amines 26100-51-6DP, Poly(lactic acid), derivs., reaction products with drugs 26124-68-5DP, Poly(glycolic acid), derivs., reaction products with drugs 27219-07-4DP, reaction products with polymer derivs. and drugs 28650-62-6DP, Poly(p-vinylbenzoyl chloride), derivs., reaction products with drugs 42042-68-2DP, reaction products with polymer derivs. and drugs 87413-09-0DP, reaction products with polymer derivs. and drugs 103057-44-9DP, reaction products with polymer derivs. and drugs 548771-40-0DP, reaction products with polymer derivs. and drugs ***548771-41-1DP***, reaction products with polymer derivs.
(controlled release pharmaceuticals containing polymer-bound drugs)

IT ***437-38-7DP***, Fentanyl, reaction products with polymer derivs.
548771-41-1DP, reaction products with polymer derivs.
(controlled release pharmaceuticals containing polymer-bound drugs)

RN 437-38-7 USPATFULL
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



RN 548771-41-1 USPATFULL
CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, tetrafluoroborate(1-) (1:1) (9CI) (CA INDEX NAME)

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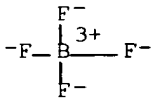
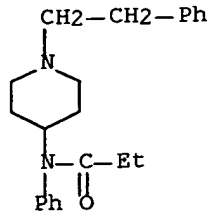
CRN 14874-70-5
CMF B F4
CCI CCS



CM 2

CRN 437-38-7

CMF C22 H28 N2 O



L112 ANSWER 54 OF 56 USPATFULL on STN
ACCESSION . . .
tannate of an opioid. Suitable opioids include alfentanil, buprenorphine, butorphanol, carfentanil, cocaine, codeine, dezocine, diacetylmorphine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, ***fentanyl***, heroin, hydrocodone, hydromorphone, β-hydroxy-3-methylfentanyl, levo-α-acetylmethadol, levorphanol, lofentanil, meperidine, methadone, morphine, nalbuphine, nalmefene, o-methylnaltrexone, naloxone, naltrexone, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene,. . .
AI US 2003-734460 A1 20031212 (10) <--
AB . . . tannate of an opioid. Suitable opioids include alfentanil, buprenorphine, butorphanol, carfentanil, cocaine, codeine, dezocine, diacetylmorphine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, ***fentanyl***, heroin, hydrocodone, hydromorphone, β-hydroxy-3-methylfentanyl, levo-α- acetylmethadol, levorphanol, lofentanil, meperidine, methadone, morphine, nalbuphine, nalmefene, o-methylnaltrexone, naloxone, naltrexone, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene,. . .
SUMM . . . that are readily commercially available such as alfentanil, buprenorphine, butorphanol, carfentanil, cocaine, codeine, dezocine, diacetylmorphine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, ***fentanyl***, heroin, hydrocodone, hydromorphone, β-hydroxy-3-methylfentanyl, levo-α-acetylmethadol, levorphanol, lofentanil, meperidine, methadone, morphine, nalbuphine, nalmefene, o-methylnaltrexone, naloxone, naltrexone, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene,. . .
SUMM . . . invention will typically additionally contain citric acid, caramel, glycerin, sorbitol solution, propylene glycol, saccharin sodium, sodium benzoate, flavoring agent and ***purified*** water.
DETD . . . with a stirrer, thermometer, dropping funnel and water bath. 412.6 g (0.83 mole) of hydrocodone bitartrate and 3.3 kg of ***purified*** water were added to the flask and the mixture was stirred at a temperature of 30-40° C. To the resultant. . . measured 12-13. The reaction mixture was allowed to settle and the supernatant liquid was decanted off. About 2 liters of ***purified*** water were added to the solid in the flask and the mixture was stirred for 15 minutes. The solid was filtered off and washed with two liter portions of ***purified*** water. The solid was sucked dry and it weighed 290.4 g. A small sample of the solid was dried under. . .
DETD . . . bath and a hot plate. The oil bath was heated to a temperature of 100-110° C. and 8 g of ***purified*** water and 34 g (0.02 mole) of tannic acid having a K.F. moisture content of 4.8% were charged

to the. . .

DETD . . . thermometer and water bath. The water bath was heated to a temperature of about 65° C. and 70 g of ***purified*** water and 100.8 g (0.056 mole) of tannic acid (K.F. moisture level of 4.8%) were charged to the beaker and. . .

DETD [0040] Example 2 is repeated using 12 g of ***purified*** water, 38 g (0.02 mole) of tannic acid (K.F. moisture content of 4.8%) and 31.5 g (0.1 mole) of oxycodone. . .

DETD [0041] Example 3 is repeated using 80 g of ***purified*** water, 114 g (0.06 mole) of tannic acid (K.F. moisture content of 4.8% and 94.5 g (0.3 mole) of oxycodone. . .

CLM What is claimed is:

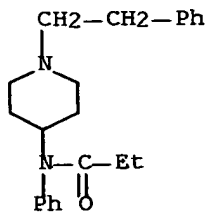
. . . is selected from the group consisting of alfentanil, buprenorphine, butorphanol, carfentanil, cocaine, codeine, dezocine, diacetylmorphine, dihydrocodeine, dihydromorphine, diphenoxylate, diprenorphine, etorphine, ***fentanyl***, heroin, hydrocodone, hydromorphone, β-hydroxy-3-methylfentantanyl, levo-α-acetylmethadol, levorphanol, lofentanil, meperidine, methadone, morphine, nalbuphine, nalmefene, o-methylnaltrexone, naloxone, naltrexone, oxycodone, oxymorphone, pentazocine, pethidine, propoxyphene,. . .

IT 50-36-2DP, Cocaine, tannate 57-27-2DP, Morphine, tannate, biological studies 57-42-1DP, Meperidine, tannate 76-41-5DP, Oxymorphone, tannate 76-57-3DP, Codeine, tannate 76-99-3DP, Methadone, tannate 77-07-6DP, Levorphanol, tannate 125-28-0DP, Dihydrocodeine, tannate 125-29-1DP, Hydrocodone, tannate 359-83-1DP, Pentazocine, tannate ***437-38-7DP***, Fentanyl, tannate 465-65-6DP, Naloxone, tannate 466-99-9DP, Hydromorphone, tannate 469-62-5DP, Propoxyphene, tannate 509-60-4DP, Dihydromorphine, tannate 561-27-3DP, Diacetylmorphine, tannate 915-30-0DP, Diphenoxylate, tannate 1477-40-3DP, Levo-α-acetylmethadol, tannate 14357-78-9DP, Diprenorphine, tannate 14521-96-1DP, Etorphine, tannate 16590-41-3DP, Naltrexone, tannate 20594-83-6DP, Nalbuphine, tannate 27203-92-5DP, Tramadol, tannate 42408-82-2DP, Butorphanol, tannate 51931-66-9DP, Tilidine, tannate 52485-79-7DP, Buprenorphine, tannate 53648-55-8DP, Dezocine, tannate 55096-26-9DP, Nalmefene, tannate 56030-54-7DP, Sufentanil, tannate 59708-52-0DP, Carfentanil, tannate 61380-40-3DP, Lofentanil, tannate 71195-58-9DP, Alfentanil, tannate 79413-55-1DP, tannate 132875-61-7DP, Remifentanil, tannate 736142-24-8DP, tannate
(opioid tannate compns.)

IT ***437-38-7DP***, Fentanyl, tannate
(opioid tannate compns.)

RN 437-38-7 USPATFULL

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



L112 ANSWER 55 OF 56 USPATFULL on STN

ACCESSION NUMBER: 2004:83172 USPATFULL Full-text
TITLE: Active agent delivery systems and methods for protecting and administering active agents
INVENTOR(S): Piccariello, Thomas, Blacksburg, VA, UNITED STATES
Kirk, Randal J., Radford, VA, UNITED STATES
Olon, Lawrence P., Bristol, TN, UNITED STATES
PATENT ASSIGNEE(S): New River Pharmaceuticals Inc. (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2004063628	A1	20040401		<--
	US 7060708	B2	20060613		
APPLICATION INFO.:	US 2002-156527	A1	20020529	(10)	<--

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-986426, filed on 8 Nov 2001, PENDING Continuation-in-part of Ser. No. US 1999-411238, filed on 4 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-265415, filed on 10 Mar 1999, ABANDONED Continuation-in-part of Ser. No. US 2000-642820, filed on 22 Aug 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	WO 2000-US5693	20000306

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUNTON & WILLIAMS, INTELLECTUAL PROPERTY DEPARTMENT, 1900 K STREET, N.W., SUITE 1200, WASHINGTON, DC, 20006-1109
NUMBER OF CLAIMS: 56
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 10108
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to active agent delivery systems and more specifically to compositions that comprise amino acids, as single amino acids or peptides, covalently attached to active agents and methods for administering conjugated active agent compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 2002-156527 A1 20020529 (10) <--
SUMM . . . N-carboxyanhydrides. In another embodiment, the peptide can be prepared through a fermentation process of recombinant microorganisms followed by harvesting and ***purification*** of the appropriate peptide. Alternatively, if a specific sequence of amino acids is desired, an automated peptide synthesizer can be. . .
DETD . . . Estradiol; Norethindrone
Ethinyl Estradiol; Norgestimate
Ethinyl Estradiol; Norgestrel
Ethylmorphine
Etidronate Disodium
Etodolac
Etoposide
Etoricoxib
Exendin-4
Famciclovir
Famotidine
Felodipine
Fenofibrate
Fenretinide

Fentanyl
Fexofenadine Hydrochloride
Filgrastim SD01
Finasteride
Flecainide Acetate
Fluconazole
Fludrocortisone Acetate
Flumanzenil
Fluorouracil
Fluoxetine
Flutamide
Fluticasone
Fluvastatin
Fluvoxamine Maleate
Follitropin Alfa/Beta

. . .

DETD . . . stirred for several hours at room temperature, the urea by-product filtered off, and the product precipitated out in ether and ***purified*** using gel permeation chromatography (GPC) or dialysis.

DETD . . . room temperature for several hours. The product is then precipitated out in ether. The crude product is suitably deprotected and ***purified*** using GPC.

DETD . . . The resulting dark solution was stirred overnight. Solvent was then removed, NaHCO.sub.3 (saturated solution) added and the crude product was ***purified*** using ultrafiltration (YM1) to obtain Furosemide-pSer (0.101 g) as a dark green solid.

DETD . . . stirred for several hours at room temperature, the urea by-product filtered off, and the product precipitated out in ether and ***purified*** using GPC or dialysis. ##STR5##

DETD . . . of polymers (Glu).sub.7-13 and (Glu).sub.5-14-cephalexin. Other chain-lengths may be present but they are not clearly visible in the MALDI spectra. ***Reversed-phase HPLC*** (265 nm detection, C18 column, 16% MeOH/4% THF/80% water mobile phase) indicated that no free cephalexin was present in the isolated material. "Water" in the ***HPLC*** actually refers to an aqueous buffer of 0.1% heptanesulfonic acid and 1.5% triethylamine.

DETD . . . evaporation under reduced pressure, yielding light brown oil. The oil was dried on the vacuum manifold and the product was ***purified*** by column chromatography on silica gel using EtOAc/Hexanes 1:5 to 1:4 solvent system. The product fractions were pooled and solvent. . .

DETD . . . evaporation under reduced pressure, yielding light brown oil. The oil was dried on the vacuum manifold and the product was ***purified*** by column chromatography on silica gel using EtOAc/Hexanes 1:5 to 1:4 solvent system. The product fractions were pooled and solvent. . .

DETD . . . methanol or i-propanol was then added and the resulting solid was collected and dissolved in NaHCO.sub.3(sat.). The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation, methanol precipitation, acetone precipitation or removal of water under. . .

DETD . . . for 6 hours and heated at 70° C. for 12 hours. Solvent was then removed and the crude product was ***purified*** over silica gel (100% CHCl.sub.3) to obtain Boc-Glu(AZT)-OtBu (1.09 g, 1.91 mmol, 51%) as a yellow foam.

DETD . . . mixture was added water (100 mL) and a precipitate of unreacted acyclovir formed. Solid was centrifuged and the supernatant was ***purified*** using ultrafiltration (YM1 membrane). Approximately 300 mL water was allowed to pass through the membrane. NMR has shown an unexpected. . .

DETD . . . (25 mL). A solid precipitate formed which was both drug-conjugate and free fexofenadine. Water was acidified and all solids dissolved. ***Purification*** using ultrafiltration (YM1 followed by YM3) and size exclusion chromatography using Sephadex-25 at pH 7 yielded poly-glu(fexofenadine) (0.010 g) as. . .

DETD [0221] Preparation was similar to poly-Glu(zalcitabine). ***Purification*** using ultrafiltration (YM1) yielded poly-Glu(stavudine) (0.089 g) as a white solid.

DETD . . . evaporation. Water was then added and the resulting solid was collected and dissolved in saturated NaHCO.sub.3. The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation (1.15 g, 48%).

DETD [0228] Preparation was similar to poly-glu(zalcitabine). ***Purification*** using ultrafiltration (YM1) yielded poly-Glu(metronidazole) (0.326 g) as a yellow solid.

DETD . . . evaporation. Water was then added and the resulting solid was collected and dissolved in saturated NaHCO.sub.3. The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation (0.965 g, 35%).

DETD . . . was allowed to heat to reflux and stirred at reflux overnight. Solvent was then removed and the crude compound was ***purified*** over silica gel (50-75% ethyl acetate in hexanes) to obtain Boc-Glu(Acetaminophen)-OtBu (0.432 g, 0.900 mmol, 72%).

DETD . . . added. The reaction was stirred for 60 hours and filtered. The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (10:1-0:1 hexane:EtOAc) to provide the target as a clear film (0.256 g, 31%). R.sub.f=0.54 (6:1 CHCl.sub.3:MeOH; .sup.1H. . .

DETD . . . was stirred for 1 hour with trifluoroacetic acid (1.5 mL). The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (8:1 CHCl.sub.3:MeOH) to yield a clear film.

DETD . . . (0.22 mL, 1.98 mmol). The solution was then refluxed for 48 hours. Solvent was then removed and crude product was ***purified*** over silica gel (25-50% ethyl acetate in hexanes). Two major products were isolated, one with R.sub.f=2-3, Boc-Glu(dipyrimadole)-OtBu, (0.57 g) and. . .

DETD . . . (100 mL) was then added and the resulting solid was collected and dissolved in saturated NaHCO.sub.3. The crude product was ***purified*** using ultrafiltration. Product was then collected from ultrafiltration using acid precipitation as a green solid (0.678 g, 32%).

DETD . . . whereupon the solution was filtered to remove the white precipitate and the solvent removed by rotary evaporation. The residue was ***purified*** by flash chromatography (10:1-2:1 hexane:EtOAc) to provide the succinimidyl ester as a clear oil (1.0 g, 59%).

DETD . . . with 2 mL CH.sub.2Cl.sub.2. The aqueous layer was dried and the residue dissolved in 1 mL H.sub.2O. The solution was ***purified*** by SEC (G-15, 10 mL dry volume) and eluted with water. Those fractions containing conjugate were combined and dried to. . .

DETD . . . stir over night at room temperature under argon. The following morning, 2.5 mL of the reaction mixture was transferred to ***separate*** flask (Flask B). T4-NCA (27 mg, 0.03 mmol) was added to the original flask (Flask A), and both solutions were. . .

DETD [0350] For Those Conjugates that Used a Protected NCA an Additional, ***Separate*** Deprotection Step was Necessary:

DETD . . . 25 mL H.sub.2O. The residue was dried in vacuum to provide Trp(Boc).sub.15-T4 as a brown solid. This material was further ***purified*** by ultrafiltration (Amicon regenerated cellulose, YM1, NMWL 1000, wash with 30 mL pH 5 H.sub.2O) to provide

[Trp(Boc)].sub.15-T4 as a. . .

DETD [0373] As in the synthesis of [Glu].sub.15-L-DOPA except 0.439 grams of GluNCA were used. The final yield of ***purified*** material was 0.007 grams.

DETD . . . was removed by rotary evaporation to provide the deprotected polymer as a brown solid (0.262 g, 91%) which was further ***purified*** by ultrafiltration (Amicon regenerated cellulose, YM1, NMWL 1000, wash with 30 mL pH 5 H.sub.2O).

DETD . . . N-dimethyl-4-aminopyridine (0.119 g, 1.0 mmol). After stirring for 18 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (30:1-8:1 CHCl.sub.3:CH.sub.3OH with 1 drop HOAc/100 mL eluent) to provide the target as a white solid (0.242. . .

DETD . . . N-dimethyl-4-aminopyridine (0.217 g, 1.8 mmol). After stirring for 16 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (30:1-8:1 CHCl.sub.3:CH.sub.3OH with 1 drop HOAc/100 mL eluent) to provide the target as a white solid (0.473. . .

DETD . . . N-dimethyl-4-aminopyridine (0.051 g, 0.42 mmol). After stirring for 21 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (12:1-0:1 hexane:EtOAc) to provide the target as a white solid (0.187 g, 55%): R.sub.f (1:1 hexane:EtOAc) 0.95;. . .

DETD . . . N-dimethyl-4-aminopyridine (0.051 g, 0.42 mmol). After stirring for 18.5 h the solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (12:1-0:1 hexane:EtOAc) to provide the target as a white solid contaminated with 1-hexadecanol (0.348 g, 90%): R.sub.f. . .

DETD . . . This suspension was cooled to 4° C., filtered and dried by high vacuum for 5 hours. This material was further ***purified*** by ultrafiltration (3,000 MW) filter using saturated sodium bicarbonate as a diluent. The product was dissolved in 10 mL of. . .

DETD . . . filtered through glasswool and washed with 20 mL EtOAc. The water was removed by lyophilization and the off white residue ***purified*** by flash chromatography (C18 CH.sub.3OH) to provide roughly a 1:1 mixture of TeocT3-β-CD (R.sub.f 7:7:5:4 EtOAc:2-propanol:NH.sub.4OH:H.sub.2O) 0.64) and unmodified (3-CD. . .

DETD . . . overnight). The product can be isolated from the solution by pouring it into water and filtering. The product can be ***purified*** using GPC or dialysis.

DETD . . . stirred for several hours at room temperature, the urea by-product filtered off, and the product precipitated out in ether and ***purified*** using GPC or dialysis.

DETD . . . cooling, reaction was placed in ether and solid was collected by filtration. Solid was suspended in pH 8 water and ***purified*** using ultrafiltration. Product was filtered and dried.

DETD . . . then allowed to stir at 20° C. for 8 hours. The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (8:1-1:1 hexane:EtOAc) to provide the conjugate as a clear film (0.038 g, 11%). R.sub.f (3:1 hexane:EtOAc): 0.22;. . .

DETD . . . under argon whereupon the solution was filtered through glass wool and the solvent removed by rotary evaporation. The residue was ***purified*** by flash chromatography (30:1-8:1 CHCl.sub.3:CH.sub.3OH) to provide the peracylated statin as a white solid (0.118 g).

DETD . . . water (3+100 mL). The organic layer was dried over MgSO.sub.4 and solvents were removed under reduced pressure. Crude product was ***purified*** over silica gel (0-10% MeOH in CHCl.sub.3) to obtain the ketal conjugate (0.010 g) in a 1:1 mixture with free. . .

DETD . . . added and the mixture washed with 5 mL saturated NaCl. The solvent was removed by rotary evaporation and the residue ***purified*** by flash chromatography (15:1:0-10:1:0-100:10:1 CHCl.sub.3:MeOH:HOAc) to provide the target as a white solid (23%).

DETD . . . was added and the reaction stirred 24 more hours. The solvent was removed by rotary evaporation and the residue repeatedly ***purified*** by flash chromatography to provide the target as a white solid (7%).

DETD . . . to remove gross particulate matter. Any remaining particulate was filtered with a 0.2 μm nylon syringe filter (Whatman) prior to ***HPLC*** analysis.

DETD [0489] Enzyme digested conjugates were analyzed for the presence of unconjugated active agent by ***reversed phase HPLC*** (C18, 4.6+250 mm, 5 μm, 300A) using the following conditions: mobile phase--Lotus buffer (4.5 mL of H.sub.3PO.sub.4, 8.8 mL triethylamine,. . .

DETD . . . Polyserine-naltrexone conjugates were tested in male Sprague Dawley rats (.about.250 g). Defined doses were delivered orally in gelatin capsules containing ***purified*** dry powder polyserine-naltrexone conjugates or naltrexone. No excipients were added to the capsules.

DETD [0531] Polyserine-naltrexone conjugates were tested in Sprague-dawley rats (250 g). Defined doses were delivered orally in gelatin capsules containing ***purified*** dry powder polyserine-naltrexone conjugates or naltrexone. No excipients were added to the capsules.

DETD . . . was removed from the monolayers and concentrated on SP-18 columns. Concentrated samples were analyzed for the presence of naltrexone by ***reverse phase HPLC***. Each Polyserine-naltrexone conjugate showed significant release of free naltrexone from the polymer conjugate in three ***separate*** samples. In conclusion, Caco-2 cellular enzymes affected release of naltrexone from Polyserine-naltrexone conjugates BB-272 and BB-301. Release of carbonate linked. . .

DETD [2299] ***Fentanyl***

DETD [2300] ***Fentanyl*** is a known pharmaceutical agent that is used in the treatment of pain. It is both commercially available and readily. . .

DETD [2301] In the present invention, the ***fentanyl*** or modified ***fentanyl*** is covalently attached to the peptide via a linker. This linker may be a small molecule containing 2-6 carbons and. . .

L112 ANSWER 56 OF 56 USPATFULL on STN

ACCESSION NUMBER: 2004:31863 USPATFULL Full-text

TITLE: Methods and compositions for reducing the development of drug tolerance and/or physical dependence

INVENTOR(S): Whistler, Jennifer, El Cerrito, CA, UNITED STATES
Zastrow, Mark von, San Carlos, CA, UNITED STATES

PATENT ASSIGNEE(S): The Regents of the University of California (U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2004024005	A1	20040205		<--
APPLICATION INFO.:	US 2003-350270	A1	20030122	(10)	<--

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-351466P	20020123 (60)
	US 2002-351442P	20020123 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C., P O BOX 458, ALAMEDA, CA, 94501
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Page(s)
LINE COUNT: 2042
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods for reducing, preventing or delaying the development of tolerance to certain drugs that target G-protein coupled receptors (GPCR). The methods are generally carried out by co-administering with the drug an agonist for the drug-target GPCR that promotes the endocytosis of the targetted receptor. The methods are particularly useful for drugs that target the opioid receptors, for example morphine. The present invention also provides compositions comprising a drug and an agonist that are advantageous in preventing the development of tolerance to the drug that can develop when the drug is administered alone.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AI US 2003-350270 A1 20030122 (10) <--

SUMM . . . the opioid drug can include morphine, and the agonist can include a mu opioid receptor agonist selected from DAMGO, methadone, ***fentanyl***, sufentanil, remi-***fentanyl***, etonitazene, and etorphine.

SUMM . . . the opioid drug can include morphine, and the agonist can include a mu opioid receptor agonist selected from DAMGO, methadone, ***fentanyl***, sufentanil, remi-***fentanyl***, etonitazene, and etorphine.

DETD . . . Preferably the agonist will be a selective mu opioid receptor agonist. Suitable agonists for this method include enkephalin, DAMGO, methadone, ***fentanyl***, sufentanil, remi-***fentanyl***, etonitazene etorphine, and dihydroetorphine. Preferably, the agonist will be selected from methadone, ***fentanyl***, sufentanil, remi-***fentanyl***, or etonitazene.

DETD . . . to, and/or physical dependence on, morphine by co-administering a mu opioid agonist. Preferred mu opioid agonists include enkephalin, DAMGO, methadone, ***fentanyl***, sufentanil, remi-***fentanyl*** , etonitazene etorphine, and dihydroetorphine. More preferred agonists include methadone, ***fentanyl***, sufentanil, remi-***fentanyl*** , and etonitazene. "Morphine" includes (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol and various derivatives, salts, hydrates, and solvates, that are useful as analgesics, including morphine hydrobromide,. . .

DETD . . . combination of these compounds are administered, they may be administered together in the same composition, or may be administered in ***separate*** compositions. If the agonist and the drug are administered in ***separate*** compositions, they may be administered by similar or different modes of administration, and may be administered simultaneously with one another,. . .

DETD . . . the mu opioid receptor other than morphine. Preferred compositions comprise morphine and one or more agonists selected from DAMGO, methadone, ***fentanyl***, sufentanil, remifentanyl, etonitazene, and etorphine, in addition to the mu opioid receptor agonists described above.

DETD . . . also provides kits including: (1) a drug that targets a GPCR and (2) an agonist for the same GPCR in ***separate*** containers. The considerations for selecting and formulating the drug and agonist (i.e., suitable carriers, doses, etc.) are the same as. . .

CLM What is claimed is:

. . . The pharmaceutical composition of claim 9, wherein the agonist comprises a compound selected from the group consisting of DAMGO, methadone, ***fentanyl***, sufentanil, remi-***fentanyl***, etonitazene, and etorphine.

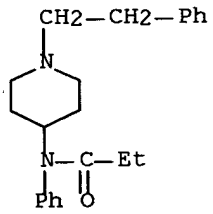
. . . 20. The method of claim 19, wherein the agonist comprises a compound selected from the group consisting of DAMGO, methadone, ***fentanyl*** , sufentanil, remifentanyl, etonitazene, and etorphine.

IT 57-27-2P, Morphine, biological studies 64-31-3P, Morphine sulfate 76-99-3P, Methadone ***437-38-7P***, Fentanyl 911-65-9P, Etonitazene 14521-96-1P, Etorphine 56030-54-7P 78123-71-4P, DAMGO 132875-61-7P, Remifentanyl
(methods and compns. for reducing development of drug tolerance and phys. dependence)

IT ***437-38-7P***, Fentanyl
(methods and compns. for reducing development of drug tolerance and phys. dependence)

RN 437-38-7 USPATFULL

CN Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]- (CA INDEX NAME)



```
=>  d his full

     (FILE 'HOME' ENTERED AT 10:04:48 ON 28 DEC 2007)

     FILE 'ZCAPLUS' ENTERED AT 10:05:35 ON 28 DEC 2007
                E US2006-574545/APPS
L1              1 SEA ABB=ON  PLU=ON  US2006-574545/AP
                D SCA

     FILE 'REGISTRY' ENTERED AT 10:08:55 ON 28 DEC 2007
L2              1 SEA ABB=ON  PLU=ON  437-38-7
                D SCA
                SEL RN
L3             56 SEA ABB=ON  PLU=ON  437-38-7/CRN
                D SCA
L4              1 SEA ABB=ON  PLU=ON  1443-54-5
                E "PROPANAMIDE, N-PHENYL-N-(1-(2-PHENYLETHYL)-4-PIPERIDINYL)-,
                E "PROPANAMIDE, N-PHENYL-N-(1-(2-PHENYLETHYL)-4-PIPERIDINYL)-,
L5              1 SEA ABB=ON  PLU=ON  "PROPANAMIDE, N-PHENYL-N-(1-(2-PHENYLETHYL)
                -4-PIPERIDINYL)-, CONJUGATE MONOACID"/CN

     FILE 'ZCAPLUS' ENTERED AT 10:13:38 ON 28 DEC 2007
L6           4334 SEA ABB=ON  PLU=ON  L2
L7             31 SEA ABB=ON  PLU=ON  L4
L8              1 SEA ABB=ON  PLU=ON  L5
L9         815720 SEA ABB=ON  PLU=ON  ?CHROMATOG?/BI
                E CHROMATOGRAPHY+ALL/CT

     FILE 'REGISTRY' ENTERED AT 10:15:51 ON 28 DEC 2007
L10             3 SEA ABB=ON  PLU=ON  L2 OR L4 OR L5

     FILE 'ZCAPLUS' ENTERED AT 10:16:01 ON 28 DEC 2007
L11             3 SEA ABB=ON  PLU=ON  L10 (L) PUR/RL
                D SCA
L12             3 SEA ABB=ON  PLU=ON  L9 AND L11

     FILE 'REGISTRY' ENTERED AT 10:17:43 ON 28 DEC 2007
L13               STR 437-38-7
L14             2 SEA FAM SAM L13
                D SCA
L15            70 SEA FAM FUL L13
                SAVE TEMP CHA545STR13L/A L15
L16            31 SEA ABB=ON  PLU=ON  L15 AND MXS/CI
L17            39 SEA ABB=ON  PLU=ON  L15 NOT L16
L18             4 SEA ABB=ON  PLU=ON  L15 AND C>22
                D SCA
                D SCA L16
L19            36 SEA ABB=ON  PLU=ON  L15 NOT (L16 OR L18)
L20            13 SEA ABB=ON  PLU=ON  L19 AND NC<2
                D SCA
L21             1 SEA ABB=ON  PLU=ON  L10 AND L20
L22            15 SEA ABB=ON  PLU=ON  L20 OR L10
L23            21 SEA ABB=ON  PLU=ON  L19 NOT L22
                D SCA

     FILE 'ZCAPLUS' ENTERED AT 10:26:06 ON 28 DEC 2007
L24        270540 SEA ABB=ON  PLU=ON  PUR/RL
L25             3 SEA ABB=ON  PLU=ON  L22 (L) L24
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L26          4354 SEA ABB=ON  PLU=ON  L22
L27           490 SEA ABB=ON  PLU=ON  L23
L28           223 SEA ABB=ON  PLU=ON  L26 AND L9
L29         12386 SEA ABB=ON  PLU=ON  REVERSED PHASE HPLC/CW
L30             8 SEA ABB=ON  PLU=ON  L26 AND L29
                  D SCA
L31         70356 SEA ABB=ON  PLU=ON  REVERS?/BI (W) PHASE#/BI
L32             3 SEA ABB=ON  PLU=ON  L27 AND L29
L33            10 SEA ABB=ON  PLU=ON  L30 OR L32
L34             2 SEA ABB=ON  PLU=ON  L33 NOT L30
                  SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 10:30:42 ON 28 DEC 2007
L35             1 SEA ABB=ON  PLU=ON  990-73-8/BI
                  D SCA
L*** DEL       36 S L26-L27

     FILE 'ZCAPLUS' ENTERED AT 10:31:36 ON 28 DEC 2007
L36          4765 SEA ABB=ON  PLU=ON  (L26 OR L27)
L37            29 SEA ABB=ON  PLU=ON  L36 AND L31
L38            64 SEA ABB=ON  PLU=ON  L36 (L) PREP/RL
L39             5 SEA ABB=ON  PLU=ON  L38 AND L9
                  D SCA
L40        195334 SEA ABB=ON  PLU=ON  HPLC/BI
L41             1 SEA ABB=ON  PLU=ON  L38 AND L40
                  D SCA
L42             1 SEA ABB=ON  PLU=ON  L31 AND L38
                  D SCA
L43            97 SEA ABB=ON  PLU=ON  L36 (L) L9
L44        187446 SEA ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
                  E CHROMATOGRAPHY, COLUMN AND LIQUID+ALL/CT
                  E E2=ALL/CT
                  E CHROMATOGRAPHY, COLUMN AND LIQUID+ALL/CT
                  E E2+ALL/CT

     FILE 'HCAPLUS' ENTERED AT 10:51:00 ON 28 DEC 2007
                  E CHROMATOGRAPHY, COLUMN AND LIQUID+ALL/CT
                  E E2+ALL/CT
L45        132461 SEA ABB=ON  PLU=ON  LIQUID CHROMATOGRAPHY+NT,OLD/CT
L46          4765 SEA ABB=ON  PLU=ON  L22 OR L23
L47            71 SEA ABB=ON  PLU=ON  L45 AND L46
L48        187446 SEA ABB=ON  PLU=ON  ?LIQUID CHROMATOG?/BI
L49           100 SEA ABB=ON  PLU=ON  L46 AND L48
L50           113 SEA ABB=ON  PLU=ON  L47 OR L49
L51        859647 SEA ABB=ON  PLU=ON  PURIF?/BI
L52       1536035 SEA ABB=ON  PLU=ON  SEPARAT?/BI
L53             2 SEA ABB=ON  PLU=ON  L50 AND L51
L54            32 SEA ABB=ON  PLU=ON  L50 AND L52
                  D SCA L53
                  D SCA L53
                  D SCA L54
L55        195334 SEA ABB=ON  PLU=ON  HPLC/BI
L56        121838 SEA ABB=ON  PLU=ON  L55 NOT L45
L57            90 SEA ABB=ON  PLU=ON  L46 AND L55
L58             4 SEA ABB=ON  PLU=ON  L57 AND L51
L59            22 SEA ABB=ON  PLU=ON  L57 AND L52
L60             5 SEA ABB=ON  PLU=ON  (L58 OR L59) NOT (L53 OR L54)
                  D SCA
L61            64 SEA ABB=ON  PLU=ON  L36 (L) PREP/RL
L62             1 SEA ABB=ON  PLU=ON  L61 AND (L45 OR L48 OR L55)
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                D SCA
L63             3 SEA ABB=ON  PLU=ON  L61 AND L51
L64             2 SEA ABB=ON  PLU=ON  L61 AND L52
L65             4 SEA ABB=ON  PLU=ON  (L63 OR L64)
                D SCA

     FILE 'USPATFULL' ENTERED AT 11:44:03 ON 28 DEC 2007

     FILE 'HCAPLUS' ENTERED AT 11:44:33 ON 28 DEC 2007
L66             TRA PLU=ON  L61 1- PN :      55 TERMS

     FILE 'USPATFULL' ENTERED AT 11:44:36 ON 28 DEC 2007
L67            12 SEA ABB=ON  PLU=ON  L66

     FILE 'HCAPLUS' ENTERED AT 11:44:54 ON 28 DEC 2007
L68             TRA PLU=ON  L61 1- AP :      49 TERMS

     FILE 'USPATFULL' ENTERED AT 11:44:55 ON 28 DEC 2007
L69            13 SEA ABB=ON  PLU=ON  L68
L70            13 SEA ABB=ON  PLU=ON  L67 OR L69
L71             2 SEA ABB=ON  PLU=ON  L70 AND L48
L72             7 SEA ABB=ON  PLU=ON  L70 AND L55
L73             5 SEA ABB=ON  PLU=ON  L70 AND L31
L74             7 SEA ABB=ON  PLU=ON  (L71 OR L72 OR L73)
                D KWIC 1-7
L75             8 SEA ABB=ON  PLU=ON  L70 AND L51
L76             8 SEA ABB=ON  PLU=ON  L70 AND L52
L77             9 SEA ABB=ON  PLU=ON  (L74 OR L75 OR L76)
L78             6 SEA ABB=ON  PLU=ON  L77 AND (L22 OR L23)
L79          4705 SEA ABB=ON  PLU=ON  FENTANYL
L80             9 SEA ABB=ON  PLU=ON  L77 AND L79

     FILE 'STNGUIDE' ENTERED AT 11:51:41 ON 28 DEC 2007

     FILE 'ZCAPLUS' ENTERED AT 11:52:10 ON 28 DEC 2007
L81          4765 SEA ABB=ON  PLU=ON  (L22 OR L23)
L82             3 SEA ABB=ON  PLU=ON  L81 (3W) SEP?/BI
                D SCA
L83             2 SEA ABB=ON  PLU=ON  L81 (3W) L52
                D SCA
L84            19 SEA ABB=ON  PLU=ON  L81 (L) L52
L85             4 SEA ABB=ON  PLU=ON  L9 AND L84
                D SCA
L86             3 SEA ABB=ON  PLU=ON  L84 AND (L29 OR L40 OR L44)
L87            17 SEA ABB=ON  PLU=ON  L11 OR L12 OR L30 OR L32 OR L39 OR L41 OR
                L42 OR L83 OR L86
                SEL RN L1

     FILE 'REGISTRY' ENTERED AT 11:56:35 ON 28 DEC 2007
L88            17 SEA ABB=ON  PLU=ON  (10035-10-6/BI OR 110-15-6/BI OR 13598-36-2
                /BI OR 144-62-7/BI OR 1443-54-5/BI OR 437-38-7/BI OR 50-21-5/BI
                 OR 64-18-6/BI OR 64-19-7/BI OR 75-05-8/BI OR 75-65-0/BI OR
                7631-86-9/BI OR 7647-01-0/BI OR 7664-38-2/BI OR 7664-93-9/BI
                OR 7697-37-2/BI OR 87-69-4/BI)

     FILE 'ZCAPLUS' ENTERED AT 11:56:41 ON 28 DEC 2007
L89            13 SEA ABB=ON  PLU=ON  L88 AND L87

     FILE 'USPATFULL' ENTERED AT 11:57:23 ON 28 DEC 2007
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     FILE 'ZCAPLUS' ENTERED AT 11:57:45 ON 28 DEC 2007
L90            4 SEA ABB=ON  PLU=ON  L87 NOT L89
                 D SCA
                 E ANTONIONI E/AU
                 E ANTONIONI A/AU
                 E ANTONINI E/AU
L91          121 SEA ABB=ON  PLU=ON  ANTONINI E/AU
L92            4 SEA ABB=ON  PLU=ON  ANTONINI EN?/AU
L93            0 SEA ABB=ON  PLU=ON  L91 AND L87
L94            0 SEA ABB=ON  PLU=ON  L15 AND L91
L95            1 SEA ABB=ON  PLU=ON  L15 AND L92
                 D SCA L92
L96            0 SEA ABB=ON  PLU=ON  L91 AND L40
L97            0 SEA ABB=ON  PLU=ON  L91 AND L44
L98            0 SEA ABB=ON  PLU=ON  L91 AND L31
L99            1 SEA ABB=ON  PLU=ON  L92 AND L40
L100           2 SEA ABB=ON  PLU=ON  L92 AND L44
L101           4 SEA ABB=ON  PLU=ON  L92 AND L31

     FILE 'USPATFULL' ENTERED AT 12:03:05 ON 28 DEC 2007
L102           9 SEA ABB=ON  PLU=ON  L71 OR L72 OR L73 OR L75 OR L76 OR L78 OR
                 L80
L103           1 SEA ABB=ON  PLU=ON  L102 AND (L91 OR L92)
L104           1 SEA ABB=ON  PLU=ON  L102 AND ANTONINI?/AU

     FILE 'HCAPLUS' ENTERED AT 12:04:08 ON 28 DEC 2007
L105           1 SEA ABB=ON  PLU=ON  (L91 OR L92) AND (L53 OR L54 OR L58 OR
                 L59)

     FILE 'STNGUIDE' ENTERED AT 12:04:27 ON 28 DEC 2007

     FILE 'REGISTRY' ENTERED AT 12:06:09 ON 28 DEC 2007

     FILE 'ZCAPLUS' ENTERED AT 12:06:13 ON 28 DEC 2007
                 D STAT QUE L92
                 D STAT QUE L95
                 D STAT QUE L96
                 D STAT QUE L97
                 D STAT QUE L98
                 D STAT QUE L99
                 D STAT QUE L100
                 D STAT QUE L101
L106           4 SEA ABB=ON  PLU=ON  L92 OR L95 OR (L96 OR L97 OR L98 OR L99 OR
                 L100 OR L101)

     FILE 'HCAPLUS' ENTERED AT 12:07:06 ON 28 DEC 2007
                 D STAT QUE L105

     FILE 'USPATFULL' ENTERED AT 12:07:17 ON 28 DEC 2007
                 D STAT QUE L103
                 D STAT QUE L104
L107           1 SEA ABB=ON  PLU=ON  L103 OR L104

     FILE 'STNGUIDE' ENTERED AT 12:07:41 ON 28 DEC 2007

     FILE 'ZCAPLUS, HCAPLUS, USPATFULL' ENTERED AT 12:07:51 ON 28 DEC 2007
L108           5 DUP REM L106 L105 L107 (1 DUPLICATE REMOVED)
                       ANSWERS '1-4' FROM FILE ZCAPLUS
                       ANSWER '5' FROM FILE USPATFULL
                 D IBIB ABS HITIND HITSTR L108 1-4
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             D IBIB ABS KWIC HITSTR L108 5

     FILE 'REGISTRY' ENTERED AT 12:08:39 ON 28 DEC 2007

     FILE 'ZCAPLUS' ENTERED AT 12:08:42 ON 28 DEC 2007
               D STAT QUE L11
               D STAT QUE L12
               D STAT QUE L30
               D STAT QUE L32
               D STAT QUE L39
               D STAT QUE L41
               D STAT QUE L42
               D STAT QUE L83
               D STAT QUE L86
               D STAT QUE L89
L109         16 SEA ABB=ON  PLU=ON  (L11 OR L12 OR L30 OR L32 OR L39 OR L41 OR
               L42 OR L83 OR L86 OR L89) NOT L106

     FILE 'HCAPLUS' ENTERED AT 12:10:07 ON 28 DEC 2007
               D STAT QUE L53
               D STAT QUE L54
               D STAT QUE L58
               D STAT QUE L59
L110         37 SEA ABB=ON  PLU=ON  (L53 OR L54 OR L58 OR L59) NOT L105

     FILE 'USPATFULL' ENTERED AT 12:10:46 ON 28 DEC 2007
               D STAT QUE L71
               D STAT QUE L72
               D STAT QUE L73
               D STAT QUE L75
               D STAT QUE L76
               D STAT QUE L78
               D STAT QUE L80
L111          8 SEA ABB=ON  PLU=ON  (L71 OR L72 OR L73 OR L75 OR L76 OR L78 OR
               L80) NOT L107

     FILE 'STNGUIDE' ENTERED AT 12:11:42 ON 28 DEC 2007

     FILE 'ZCAPLUS, HCAPLUS, USPATFULL' ENTERED AT 12:11:51 ON 28 DEC 2007
L112         56 DUP REM L109 L110 L111 (5 DUPLICATES REMOVED)
                    ANSWERS '1-16' FROM FILE ZCAPLUS
                    ANSWERS '17-48' FROM FILE HCAPLUS
                    ANSWERS '49-56' FROM FILE USPATFULL
               D IBIB ABS HITIND HITSTR L112 1-48
               D IBIB ABS KWIC HITSTR L112 49-56


     FILE HOME

     FILE ZCAPLUS

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FILE COVERS 1907 - 28 Dec 2007 VOL 148 ISS 1
FILE LAST UPDATED: 27 Dec 2007 (20071227/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 DEC 2007 HIGHEST RN 959655-61-9
DICTIONARY FILE UPDATES: 27 DEC 2007 HIGHEST RN 959655-61-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

FILE HCAPLUS

FILE COVERS 1907 - 28 Dec 2007 VOL 148 ISS 1
FILE LAST UPDATED: 27 Dec 2007 (20071227/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Dec 2007 (20071227/PD)
FILE LAST UPDATED: 27 Dec 2007 (20071227/ED)
HIGHEST GRANTED PATENT NUMBER: US7313828
HIGHEST APPLICATION PUBLICATION NUMBER: US2007300346
CA INDEXING IS CURRENT THROUGH 27 Dec 2007 (20071227/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Dec 2007 (20071227/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Oct 2007
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Oct 2007

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      FILE STNGUIDE
      FILE CONTAINS CURRENT INFORMATION.
      LAST RELOADED: Dec 21, 2007 (20071221/UP).

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